86-1318

No. 86-

In the Supreme Court

OF THE

United States

OCTOBER TERM, 1986

MONOCLONAL ANTIBODIES, INC.,
Petitioner,

v.

HYBRITECH, INC.,
Respondent.

PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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QUESTIONS PRESENTED

(1) Did the Federal Circuit, in reversing the trial court, misapply the "clearly erroneous" standard of Rule 52(a), as interpreted in *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564 (1985), by reinterpreting and reweighing the testimony and documentation relied upon by the trial court?

This includes the subsidiary questions:

(a) Specifically, did the Federal Circuit violate Rule 52(a) in its treatment of, for example, the conception date of the patented invention, based on its own interpretation of the underlying evidence, which was directly contrary to that of the trial court?

(b) Did the Federal Circuit violate Rule 52(a) by evaluating, disagreeing with, and giving no weight to the witness credibility determinations of the trial court?

(2) Is the Federal Circuit's decision contrary to *Hotchkiss v. Greenwood*, 52 U.S. 248 (1851), which was codified in the 1952 patent statute, 35 U.S.C. § 103 (non-obviousness), and iterated in *Graham v. John Deere Co.*, 383 U.S. 1 (1966)?

This includes the subsidiary questions:

(a) Was the Federal Circuit incorrect in holding that the trial court improperly focused on the substitution of an improved yet well known element into an existing well known process in determining non-obviousness?

(b) Did the Federal Circuit, by giving no evidentiary value to evidence which it labelled as "obvious to try" evidence, properly apply § 103?

(3) Was it proper for the Federal Circuit to make factual findings on issues either not addressed by the trial court or if addressed, held inadequate, in light of *Pullman-Standard v. Swint*, 456 U.S. 273 (1982) and *Icicle Seafoods, Inc. v. Worthington*, 106 S.Ct. 1527 (1986) which state the appropriate procedure is to remand?

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Petitioner Monoclonal Antibodies, Inc. ("MAB") respectfully prays that a Writ of Certiorari issue to review the judgment of the United States Court of Appeals for the Federal Circuit ("the Federal Circuit").

OPINIONS BELOW

The Federal Circuit opinion is reported at 802 F.2d 1367 (Fed. Cir. 1986). It is reproduced in Appendix A, (Appx.) (A1-32). The opinion of the trial court following a 15-day bench trial is reported at 623 F.Supp. 1344 (N.D. Cal. 1985) and is reproduced in Appx. B (A33-55).

JURISDICTION

The 47 page decision of the Federal Circuit was entered on September 19, 1986 (Appx. C, A56), and rehearing was denied

on November 7, 1986 (Appx. D, A57). This Court has jurisdiction under 28 U.S.C. § 1254(1).

CONSTITUTIONAL PROVISIONS, STATUTES, AND RULES INVOLVED

This case involves Amendment V, (Due Process), and Article I, Section 8, Clause 8 of the U.S. Constitution, 35 U.S.C. §§ 102 and 103, and Rule 52(a), Fed. R. Civ. P. Pertinent portions of these authorities are reproduced in Appx. F, A59-60.

STATEMENT OF THE CASE

A. Introduction to Technology

This case is based upon biotechnology, a rapidly expanding field which is becoming vital to the health care of mankind and one in which the industry is convinced patents will play a critical role.

Both parties to this action market medical test kits for the detection of substances called "antigens" within the human body, using antibodies which bind to and thereby identify the antigens. In the course of everyday life, human and animal bodies can harbor substances termed antigens, such as viruses, IgE (immunoglobulin E) indicating an allergic condition, and hCG (human chorionic gonadotropin) indicating pregnancy.

In response to an antigen, identical cells descended from a common parent, called "clones," produce identical antibodies. These antibodies, because they are produced from a single clone, are called monoclonal antibodies (monoclonals). An antibody recognizes, binds to, and combats the antigen in an immunological reaction. Such antibodies help to make up the human body's defense system. The body's blood serum contains a mixture of antibodies from many (poly) "clones," hence the name "polyclonals" or "polyclonal antibodies."

The binding strength (stickiness) of the antibody for the antigen is referred to as the antibody's "affinity," and is estimated in units of liters/mole (1/m).

The parties' test kits employ antibodies which react with and specifically detect a particular antigen in a blood or urine sample. This type of test is termed an immunoassay. It can determine, for example, whether a woman has hCG antigen, indicating pregnancy.

Until recently, monoclonals were virtually impossible to obtain, let alone mass produce for commercial use. Therefore, the scientific community used polyclonals in the test kits. They were produced by injecting a specific antigen into an animal's bloodstream and extracting the polyclonals produced in response to the antigen. Unfortunately, there are significant problems in relying upon this source: If the animal dies, the source of antibodies is gone; different animals produce different antibodies which are specific for, and bind to different antigens; and, changes in a given animal's immune system can alter the antibodies produced. Thus, the supply of polyclonals is limited and uncertain in quality.

Scientists knew that if monoclonals could be mass produced in the laboratory, the limited supply and non-homogeneity problems would be overcome. The concept of mass producing monoclonals was only a dream until Drs. Kohler and Milstein developed a process capable of doing so, which was published in their classic paper in 1975. In recognition of this revolutionary advance in biotechnology, they were awarded a Nobel Prize in 1984.[1] As a result of the Kohler/Milstein development, it became possible to produce tailor-made monoclonals, highly specific for antigens, in vast quantities and consistent supply. In short, this process transformed the immunoassay test kit industry.

Initially, the parties applied the Kohler/Milstein technology to produce and sell monoclonals for research and development. Later, they employed the technology to develop immunoassay test kits, known as sandwich assays, employing monoclonals. These

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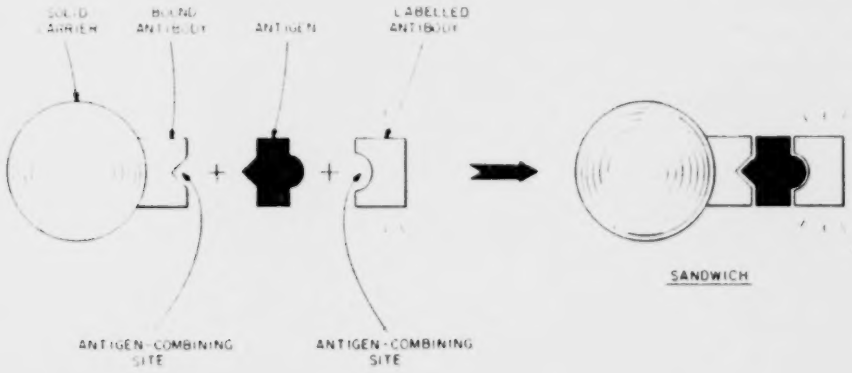
[1] Briefly, they took a tumor of a cancer cell line capable of growing *in vitro* (outside the body) and fused it with normal antibody producing cells (capable of growing only in the body or *in vivo*) to form hybrid cells (called hybridomas) which could grow *in vitro* to produce the normal antibodies. Such antibodies being produced from a single clone are termed monoclonal antibodies.

test kits are utilized throughout the world, for medical diagnostic purposes.

A sandwich assay using polyclonals was well known for many years prior to the Kohler/Milstein work. In a typical sandwich assay, a quantity of unlabelled antibody is bound to a solid support surface, such as the inside wall of a test tube, and is exposed to a fluid sample containing the antigen to be detected and a labelled antibody. The labelled antibody is detected as an indication of the presence of the antigen. The name of the assay derives from the fact that, as the Federal Circuit stated in its opinion, the resultant reaction forms a three-part complex referred to as a sandwich, having antibody bread and antigen filling. The figure below illustrates the "sandwich" concept.



B. Hybritech's U.S. Patent No. 4,376,110

On August 4, 1980, the patent application which issued into the 4,376,110 patent (the '110 patent) in suit was filed with the U.S. Patent and Trademark Office (Patent Office) naming as its inventors, Gary S. David and Howard E. Greene, two Hybritech employees (A61-81). It broadly claimed the sandwich assay process using monoclonal antibodies of affinity at least 10^8 1/m, as explained above, for determining the presence of antigens.[2]

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[2] The '110 patent is reproduced in Appx. G (A61-81). The broadest claim of that patent is Claim 19. The patent claims are at the end of the patent document and specifically define the scope of patent protection. 35 U.S.C. § 112, second paragraph.

After the patent claims were twice rejected by the Patent Examiner, (Examiner) he subsequently allowed the patent application to issue as a U.S. patent citing his Reasons for Allowance.[3] The trial court found the Examiner's reasons were "misplaced," "incorrect" and "not scientifically valid." (A43, 45)

Even though a patent is granted by the Patent Office, the courts will hold it invalid, and thus null and void, if it does not meet certain statutory conditions of patentability. Three basic conditions or hurdles of patentability which an invention must clear in order to be upheld as valid by the trial court are (1) usefulness (§ 101), (2) novelty (§ 102)[4] and (3) nonobviousness (§ 103).[5]

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[3] Typically, negotiations (called prosecution) take place between an applicant and the Examiner prior to issuance of a U.S. patent, during which the claims are often amended to include limitations to distinguish from the existing technology. Such limitations narrow the scope of protection granted by the patent. Arguments are also submitted by the applicant, as here, explaining why the amended claims define a patentable invention. In recent years, Examiners have been encouraged to make a written record of their reasons for withdrawing rejections.

As reflected in the prosecution history, the Examiner saw fit to articulate the bases upon which he withdrew his rejections of the claims and allowed the patent application to issue as the patent in suit. They were:

1. An amendment specifying that the monoclonals in the sandwich assay have an affinity (stickiness) *of at least* 10^8 *1/m*; (Emphasis added.) and,

2. A Hybritech employee's declaration alleging certain advantages in using monoclonals, rather than polyclonals, in sandwich assays (A42-43).

[4] An invention is not new (or novel), i.e. anticipated, if it existed in a single item of prior art. In this case, the trial court found the invention claimed in the '110 patent was not new because it had already been invented at the LaJolla Cancer Research Foundation.

[5] Even though an invention is not fully disclosed in a single item of prior art it would still not be patentable if the differences between the invention and the prior art are such that the invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art.

Nonobviousness, an important issue in this case, is the most frequently litigated and dispositive condition of patentability.

The trial court held the patent on David's invention, a monoclonal sandwich assay, invalid because it was neither new nor non-obvious in view of the relevant prior art (A45-46, 54-55).

The term "prior art" as used in § 103 refers to public domain technology identified by the different subsections of § 102. It is necessary to evaluate an invention against the prior art, even if the invention is "new." This insures patents are not granted on inventions which would "remove existent knowledge from the public domain, or restrict free access to materials already available" and thus fail to "promote the Progress of . . . useful Arts" as required by the Constitution. *Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966).

In determining what technology is to be considered as prior art it is necessary to identify the date the inventor completed his invention (i.e., either actually "reduced it to practice" or did so "constructively" by filing a patent application fully disclosing it). However, the date the inventor conceived the complete claimed invention[6] is also taken into account under § 102(g), which defines special rules for determining the priority of one inventor relative to another. The invention which is both first conceived and first reduced to practice is always prior art to the other, assuming it was not concealed, suppressed, or abandoned. The prior invention need not have been patented or the subject of a printed publication. *Corona Cord Tire Co. v. Dovan Chemical Corp.*, 276 U.S. 358, 381-384 (1928).

Moreover, under § 102(g), the invention first conceived but last to be reduced to practice will be adjudged "prior" if its inventor shows *sufficient and continual diligence* in reducing the invention to practice from a time starting prior to the other party's reduction to practice. Under these facts, the inventor first to conceive the invention is entitled to an earlier date of invention

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[6] Conception of the claimed invention requires the inventor to have been in possession of every feature of the invention claimed in the patent at the time of the alleged conception.

even though he was last to reduce the invention to practice. Regardless of the date of conception, an inventor, without diligence, is limited to his date of reduction to practice as his earliest invention date. These are historically well-settled principles of U.S. patent law codified in § 102(g), but typically difficult to apply.

In this case, the trial court found Hybritech's inventors had reduced the claimed invention to practice for the first time on May 6, 1980, three months prior to the patent application filing date. It held there was "no credible evidence" of conception prior to that date (A40-42, 46). Thus, diligence was not an issue. Consequently, the trial court relied upon certain events prior to May 6, 1980 as prior art in determining the novelty and obviousness of David's invention.

Based on the relevant technology which existed as prior art before May 6, 1980, the trial court held a sandwich assay using monoclonals of the claimed stickiness (affinity) was not new because it had already been invented by the work of La Jolla Cancer Research Foundation (LJCRF) in November 1979 (A45-46, 53, 55). It also concluded David's invention would have been obvious on the basis of alternative combinations of prior art (A45-46, 50-53).

Overall, the trial court held the '110 patent invalid on three additional grounds for a total of five separate statutory bases (A55).

The Federal Circuit reversed the trial court on all grounds (A32). In order to do so, it held the inventors conceived the claimed invention as of January 1979 (A16-19). Furthermore, the Federal Circuit *sua sponte* found the inventors *diligent* from conception until the filing of their patent application, *a period of 19 months* later (A19-20). By finding Hybritech to be entitled to the earlier date of invention, the Federal Circuit held the existing technology relied on by the trial court could not be considered as prior art. Thus, the Federal Circuit upheld the patent on an invention which the trial court held to be the property of the public.

ARGUMENT

I

REASONS FOR GRANTING THE PETITION

The Federal Circuit's reversal of the trial court's holding of invalidity of the '110 patent, based on a total disregard of Rule 52(a), Fed. R. Civ. P., warrants issuance of MAB's Petition for a Writ of Certiorari.

The Federal Circuit, while paying lip service to Rule 52(a) and to this Court's decision in *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564 (1985), reversed the trial court's findings which were based primarily on witness testimony. More specifically, the Federal Circuit's conclusions as to credibility and interpretation of documentation were *directly contrary* to those of the trial court.[7]

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[7] Applying Rule 52(a) appears to be uniquely difficult for judges on the Federal Circuit who made the transition in 1982 from the predecessor Court of Customs and Patent Appeals (CCPA) which applied a *de novo* standard of review, as opined by Judge Rich, the author of the Federal Circuit opinion in this case:

> One of the things that changed in the transition from CCPA to [Federal Circuit] CAFC is much greater emphasis in the new court on standard of review. I can't tell you quantitatively how much difference it makes, I can only tell you that there is more attention to it and if your case is going to turn on one or more fact findings, beware!. . . .
>
> In the CCPA, we were not reviewing trials, and Rule 52(a) was not applicable. Or if it was, we ignored it. Reviewing the PTO Boards, our attitude was we reversed them if they were wrong . . . . Meanwhile, the criticism I hear of the CAFC most often is that we have been doing *de novo* fact finding in delving into the record on our own when we should not. I am probably one of the offenders. But I have to say I do not know how one can decide whether a finding of fact is clearly erroneous without delving into the record and surely we have the right to make such a decision. I also must say that I have great difficulty in determining the distinction between an alleged fact being wrong and being "clearly erroneous," and I seem to remember a learned colleague saying "It doesn't matter; if you want to upset the fact finding, you just have to use the magic words."
>
> * * *
>
> Judge your chances on appeal accordingly.

AIPLA Quarterly Journal, Vol. 14, No. 3, at pps. 148-149.

After reevaluating the witnesses, the Federal Circuit reversed the trial court's fact findings regarding conception and reduction to practice of the '110 invention (A16-19). The result was that the Federal Circuit found inventors David and Greene entitled to a January 1979 date of invention (A19) for determining the prior art against which the invention should be evaluated. This prevented the invention from being evaluated against the same public domain technology (prior art) relied on by the trial court. To illuminate the magnitude of the Federal Circuit's disregard of Rule 52(a), we focus on three examples, *infra*.

The Court should also grant the Petition for Certiorari in this case because the Federal Circuit has effectively ignored this Court's precedent on the issue of patentability in *Hotchkiss v. Greenwood*, 52 U.S. 248 (1851), which was codified in the 1952 Patent Act, 35 U.S.C. § 103, and emphasized in *Graham v. John Deere, supra*.

Finally, this Court should grant Certiorari because the Federal Circuit, inconsistent with this Court's decision in *Icicle Seafoods, Inc., v. Worthington*, 106 S.Ct. 1527 (1986), substituted its own findings for those of the trial court it found to be inadequate. The present case is even more egregious than *Icicle Seafoods* in that the Federal Circuit went so far as to make *de novo* findings on disputed issues which were intentionally not addressed by the trial court, contrary to *Pullman-Standard v. Swint*, 456 U.S. 273 (1982). The appropriate remedy in both situations was to remand for more complete findings and conclusions.

II

THE FEDERAL CIRCUIT INCORRECTLY APPLIED THE STANDARD OF REVIEW MANDATED BY RULE 52(a), FED. R. CIV. P.

Rule 52(a) recognizes and rests upon the unique opportunity afforded the trial judge to evaluate the credibility of the witnesses and to weigh the evidence. *Inwood Laboratories, Inc. v. Ives Laboratories, Inc.*, 456 U.S. 844, 855 (1982). As recently explained by this Court in *Anderson:*

> The trial judge's major role is the determination of fact, and with experience in fulfilling that role comes expertise. Duplication of the trial judge's efforts in the court of appeals would very likely contribute only negligibly to the accuracy of fact determination at a huge cost in diversion of judicial resources. In addition, the parties to a case on appeal have already been forced to concentrate their energies and resources on persuading the trial judge that their account of the facts is the correct one; requiring them to persuade three more judges at the appellate level is requiring too much. As the Court has stated in a different context, the trial on the merits should be "the 'main event' . . . rather than a 'tryout on the road.' " [Citations omitted.]

470 U.S. at 574.

Because of the deference due the trial judge, an appellate court *must* accept the trial court's findings unless it is left with the "definite and firm conviction that a mistake has been committed." *Inwood,* 456 U.S. at 855; *United States v. United States Gypsum Co.,* 333 U.S. 364, 395 (1948).[8] In other words:

> If the district court's account of the evidence is plausible in light of the record viewed in its entirety, the court of appeals may not reverse it even though convinced that had it been sitting as the trier of fact, it would have weighed the evidence differently. Where there are two permissible views of the evidence, the factfinder's choice between them cannot be clearly erroneous. [Citations omitted.]

Anderson, 470 U.S. at 573-574.

In *Icicle Seafoods, supra,* a case factually similar to our own, this Court observed that the trial court's findings were not mentioned, discussed or analyzed by the appellate court which independently reviewed the record and made its own findings and

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[8] "To permit courts of appeals to share more actively in the fact-finding function would tend to undermine the legitimacy of the district courts in the eyes of litigants, multiply appeals by encouraging appellate retrial of some factual issues, and needlessly reallocate judicial authority." Advisory Committee Note, 1985 Amendment to Rule 52(a).

concluded: "We think that the Court of Appeals was mistaken to engage in such factfinding." 106 S.Ct. at 1530.

In fact, this Court in *Panduit Corp. v. Dennison Mfg. Co.*, 106 S.Ct. 1578 (1986), recently granted a petition for writ of certiorari, vacating a Federal Circuit decision which reversed a trial court judgment of patent invalidity for obviousness. The underlying basis for vacating was that the Federal Circuit opinion did not conform to Rule 52(a). See also, *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082 (Fed. Cir. 1985), *aff'd on remand*, No. 85-1144 (Fed. Cir. Jan. 23, 1987). Yet, even in light of that remand, the Federal Circuit has continued to disregard Rule 52(a), to even more extreme lengths, as evidenced by this case.

A. The Federal Circuit Misapplied Rule 52(a) In Overturning The Trial Court's Findings On Conception, Based On Its Own Evaluation Of The Evidence

The Federal Circuit's reversal of the trial court's findings on conception of the '110 invention is critical to the outcome of this action.[9]

Conception of the claimed invention is established by showing the inventor had a definite and permanent idea of the complete and operative invention. *Coleman v. Dines*, 754 F. 2d 353, 359

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[9] The trial court found that the claimed subject matter of the '110 patent was neither conceived nor actually reduced to practice prior to May 1980 (A40-41, 46, 48). Based on that "date of invention" the trial court concluded that the claimed subject matter was invalid because it had already been invented by researchers at LJCRF in November 1979 and was obvious in light of other public domain technology (A45, 55).

The Federal Circuit reversed the trial court, holding that Hybritech conceived the claimed invention by January 1979, and was diligent up to its constructive reduction to practice by filing the '110 application on August 4, 1980 (A18-20). The Federal Circuit also held LJCRF did not reduce the invention to practice in November 1979 and therefore concluded it was not prior art (A8-9, 19-21). These holdings, in effect, eliminated two of the trial court's grounds of invalidity of the '110 patent, obviousness and novelty, because the Federal Circuit refused to consider the most relevant prior art relied on by the trial court.

(Fed. Cir. 1985); *Gunter v. Stream*, 573 F.2d 77, 80-81 (CCPA 1978):

> It is settled that in establishing conception a party must show possession of *every feature* cited in the count [claim], and that *every limitation* of the count [claim] must have been known to the inventor at the time of the alleged conception. [Emphasis added.]

Coleman, 754 F.2d at 359, citing with approval, *Davis v. Reddy*, 620 F.2d 885, 889 (CCPA 1980).

The earliest physical evidence of conception presented by Hybritech and relied upon by the Federal Circuit was a January 4, 1979 laboratory notebook entry by inventor David (A16-17). However, this entry made *no mention* of either a monoclonal sandwich assay or a monoclonal antibody affinity of at least 10^8 1/m, two critical elements of the claimed invention.[10] Thus, the notebook entry by itself was legally incapable of supporting a holding of conception since it did not establish possession of each element of the invention in the '110 claims. *Coleman*, 754 F.2d at 359. Hybritech needed to present other evidence in order to prove conception of the *entire invention* as of January, 1979.

For example, inventor David testified that the claimed invention, in effect, was conceived in January 1979. Yet, he inconsistently maintained, when questioned on specifics, that in January, 1979, Hybritech was unaware of the claimed affinity limitation and that until mid-1979, Hybritech did not even have monoclonals. The trial court simply did not believe David and chose not to name him in a list of credible witnesses included in its opinion (A47). This credibility finding was independently prepared by the trial court (A95).[11]

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[10] As set forth in Footnote 3, the addition of the affinity limitation to the claims was an important basis underlying the issuance of the patent.

[11] Reproduced in Appx. H, (A82-104) is the trial court opinion, with portions independently prepared by the trial court underlined and asterisks indicating deletions from the proposed findings and conclusions submitted by MAB.

Ignoring the trial court's omission of David from its list of credible witnesses, the Federal Circuit relied extensively on David's testimony in holding that a monoclonal sandwich assay had been conceived at Hybritech in January 1979. In fact, in the three pages devoted to this issue the Federal Circuit specifically referred to and relied upon David's testimony nine separate times (A16-19).

* * *

The Federal Circuit, realizing it was relying almost exclusively upon witness testimony to support its holding of conception, added: "Hybritech laboratory notebooks and the nature of Hybritech's research program fully corroborate the testimonial evidence of conception" by Greene, David and Adams that using monoclonals in a sandwich assay was conceived before the LJCRF work (A16).

In effect, the Federal Circuit was citing documentary evidence to support its credibility evaluations of the witnesses not listed as credible by the trial court. Rather than determining whether the trial court was clearly erroneous, the Federal Circuit was concerning itself with *whether its de novo* findings based on its own witness evaluations *were clearly supported.*

The trial court considered Hybritech's research program and found as of early 1979, Hybritech had "not yet decided exactly what they would be doing regarding monoclonal antibodies in diagnostics." (A40)

The Federal Circuit conceded that conception was "sparsely documented" at Hybritech (A16). Yet, it still found the trial court's evaluation of that documentation to be clearly erroneous and excused Hybritech's weak documentation because it was a start-up company (A16, 18-19). It found, "there is no doubt that exploiting monoclonal antibodies for use in sandwich assays was one of the major objectives of Hybritech." (A16) Such evaluation as to weight to be given admittedly "sparse documentation" should reside exclusively with the trial court, and is outside the scope of Rule 52(a).

* * *

The trial court considered minutes of Hybritech's scientific meetings covering ten months of research on a wide range of subjects. It concluded there was no credible documentation prior to May, 1980, of when a monoclonal sandwich assay was conceived by Hybritech (A40,46,48). In fact, these minutes *never mentioned* the use of monoclonals of any affinity in a sandwich assay.

After reviewing the record, the Federal Circuit held Hybritech's minutes in early 1979, "contained little" regarding the invention's claimed subject matter (A16). This finding, contrary to the evidence, with no citation to record, was used by the Federal Circuit *to support its reversal* of the trial court's finding.

The Federal Circuit's reliance on testimony, not listed as credible, and documentation such as notebook entries and Hybritech's minutes, which alone were legally insufficient to conclude conception could have occurred in January 1979, is a far cry from the "clearly erroneous" standard of review which requires a "definite and firm conviction that a mistake has been committed." *United States Gypsum*, 333 U.S. at 395.

* * *

In addition, the Federal Circuit relied upon a letter from Greene to Pharmacia Fine Chemicals, dated April 26, 1979 (A16). The trial court, for good reason, did not cite in its opinion this letter, which merely referred to Hybritech's:

> [e]fforts to bring the new exciting hybridoma technology into routine medical use . . . [and its exploration of] several intriguing concepts for which monoclonals may open up new immunodiagnostic techniques heretofor infeasible with animal serums. [A16]

The Federal Circuit's interpretation of this letter to support its evaluation of testimony is illogical (A16). Sandwich assays with animal serums (polyclonals) were not only feasible but were in commercial use prior to that letter. This further exemplifies the Federal Circuit's fervor to find corroboration for the testimony of Greene and David, whom the trial court did not list as credible.

* * *

The Federal Circuit, further holding the trial court to be clearly erroneous, found: "[t]he claimed affinity limitation of at least about 10^8 liters/mole was determined and appreciated during the course of the development of the claimed subject matter." (A18) Yet Hybritech's documentary evidence alone, was legally incapable of supporting the Federal Circuit's finding, since during a time relevant to the conception date there was no link whatsoever between the affinity limitation and a sandwich assay. The Federal Circuit had to have relied heavily on witnesses who were not listed as credible by the trial court to support this finding, a clear violation of Rule 52(a).

B. The Federal Circuit Misapplied Rule 52(a) In Overturning The Trial Court's Findings On Prior Invention By LJCRF Based On Its Own Evaluation Of The Evidence

The Federal Circuit's circumvention of Rule 52(a) is also glaringly apparent in its treatment of the trial court's finding that LJCRF had already invented (reduced to practice) a monoclonal sandwich assay before Hybritech (A41, 45-46, 53). This finding allowed the trial court to consider the work at LJCRF in evaluating the patentability of the claimed invention.

Based on the live testimony of Dr. Ruoslahti, the trial court found that LJCRF ran a successful sandwich assay using monoclonal antibodies of the claimed affinity (reduction to practice) no later than November 5, 1979 (A41, 45-46, 53). In other words, the trial court found that David was not the first inventor of the sandwich assay claimed in his '110 patent.

The Federal Circuit held the trial court's evaluation of and *reliance* upon that testimony to be clearly erroneous because it believed there was insufficient documentary support (A20). The Federal Circuit fails to understand a trial court needs *no* documentary support if it believes a witness, especially one like Dr. Ruoslahti, who is a leading scientist in the area of biotechnology. The trial court went so far as to list Ruoslahti as credible in its opinion (A47).

The Federal Circuit's unbalanced and biased treatment of the evidence is apparent. On one hand, the Federal Circuit relies on testimony (of witnesses not listed as credible by the trial court) to support its holding of Hybritech's conception and corroborates that testimony with only the "general nature" of Hybritech's research program and the legally insufficient January 1979 notebook entry, Pharmacia letter, and Hybritech minutes (A16). On the other hand, the Federal Circuit rejects as inadequate LJCRF's testimony (from witnesses found credible by the trial court) of prior reduction to practice because of the scarcity of documentary corroboration (A20).[12] The only consistency is that

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[12] A brief aside into the merits is warranted. As set forth *supra*, Section IIA, Hybritech brought forth very little corroborating evidence to support conception. The January 1979 notebook entry did not mention either monoclonals or the affinity limitation and so was missing two elements of the "invention." The minutes of Hybritech's scientific meetings do not mention the invention. Greene's letter makes no mention of the invention just "intriguing techniques." Yet, contrary to the trial court the Federal Circuit found the foregoing adequate corroboration of conception of the invention (A16-19).

In marked contrast, the Federal Circuit found the following corroborating evidence to be inadequate to support LJCRF's reduction to practice: written instructions from Ruoslahti to Uotila to carry out a monoclonal sandwich assay (which the Federal Circuit asserts "indisputably is not the claimed invention" but does not explain why it is not) and a graph (p.43D, mentioned in the Federal Circuit Opinion; see A9) showing on its face that a successful monoclonal sandwich assay had been run. Consistent therewith, Ruoslahti testified that in September-October 1979 he instructed Uotila, a researcher in his laboratory, to carry out a sandwich assay using monoclonal antibodies (A8-9). Following those instructions, Uotila successfully performed and reduced to practice a monoclonal sandwich assay (A9). The evidence further showed the research program continued and later successful sandwich assays were performed. Although the affinity of the monoclonals used was not calculated at the time the sandwich assays were run, Ruoslahti testified that later calculations showed the affinities of the monoclonal antibodies used in the assays to be greater than 10^8 1/m (A9, trial testimony). Thus, this testimony, evidencing LJCRF's conception and reduction to practice of the invention in November 1979, was consistently corroborated by documentary evidence.

the Federal Circuit reversed the trial court based on its own interpretation of the witnesses' credibility in both instances.

A "smoking gun" example of the Federal Circuit's violation of Rule 52(a) is shown by its handling of Ruoslahti's testimony:

> We also note, as evidence *bearing upon the credibility of Ruoslahti's testimony* (that LJCRF actually reduced the claimed invention to practice in 1979), that when LJCRF attempted to provoke an interference in the PTO with Hybritech . . . LJCRF could not demonstrate even a *prima facie* reduction to practice prior to Hybritech's August 4, 1980, filing date. During that proceeding, the earliest dates Ruoslahti set down on paper to support conception and reduction to practice were in 1980. [Emphasis added.] [A20-21]

The Federal Circuit also discounted Ruoslahti's testimony based on an alteration of an important notebook page in the record (A20).

Both facts are material to only one issue: whether the trial court should have believed Ruoslahti. The Federal Circuit improperly attacked the trial court's evaluation of Ruoslahti *as a witness*, which is specifically within the province of the trial court, not the appellate court. *Anderson*, 470 U.S. at 575; *Inwood*, 456 U.S. at 855-857.

C. The Federal Circuit Misapplied Rule 52(a) in Overturning The Trial Court's Findings On Commercial Success Based On Its Own Interpretation Of The Evidence

The Federal Circuit's disregard of Rule 52(a) in its evaluation of the evidence relating to commercial success is the icing on the cake. In order for commercial success to be considered as evidence of nonobviousness, Hybritech had to prove a *nexus* between its sales and the patented invention (A48). *Simmons Fastener Corp. v. Illinois Tool Works*, 739 F.2d 1573, 1575 (Fed. Cir. 1984), *cert. den.*, 471 U.S. 1065 (1985).

The trial court found Hybritech did not prove the required nexus (A48). Rather, it properly found the relatively sudden availability of monoclonals, due to the Kohler/Milstein discovery,

was a reason for Hybritech's commercial success with its sandwich assay kit (A53-55). That discovery made possible the test kit, with its predicted advantages. It still took Hybritech, the first company founded to exploit Kohler/Milstein's discovery, three years from its founding to get a kit on the market. Therefore, the trial court's finding was plausible because it took three years lead time, as illustrated by Hybritech's experience.

The Federal Circuit reversed, holding the trial court's findings of "sudden" availability unsupported by the record, because monoclonals were available in the United States for three years (A25-27). But, the Federal Circuit overlooked the required lead time.

Exactly the same evidence relied on by the trial court in finding monoclonals were suddenly available was relied on by the Federal Circuit in reaching the opposite conclusion. The Federal Circuit simply *interpreted* that evidence in a totally different manner than the trial court.

The above examples represent the tip of the iceberg in showing the Federal Circuit's massive violations of Rule 52(a). It did so as well with respect to other important issues, such as its treatment of prior art disclosed by two other researchers in the field, V.T. Oi and L.A. Herzenberg, who also testified at trial.

Despite the Federal Circuit's statements to the contrary, an informed review of its decision shows that it did not perform the function of an appellate court consistent with Rule 52(a).

III

THE FEDERAL CIRCUIT'S IMPLICIT CRITICISM OF THE TRIAL COURT'S ADOPTION OF SELECT PROPOSED FINDINGS AND CONCLUSIONS IS LEGALLY UNWARRANTED

The Federal Circuit noted this Court has held findings and conclusions adopted by the trial court are entitled to full deference under Rule 52(a) (A12-14). Yet, the Federal Circuit, after mentioning that the trial lasted three weeks, involved 30 witnesses and generated over 2,000 pages of transcript, impliedly criticized

the trial court, stating that it used "nearly verbatim Monoclonal's *pre-trial* brief and *pre-trial proposed* findings of fact and conclusions of law" and produced its opinion "in three days." (A6) There was absolutely no reason for these statements other than to disparage the trial court's prompt handling of its decision. In any event, the statement of verbatim adoption of findings is inaccurate, as the trial court's opinion contained many of its own findings and conclusions (App. H; n. 11).

The Federal Circuit may have taken a different view if it were apprised of the closing remarks of the conscientious trial court judge, Judge Conti, on the last day of trial:

> I always have the philosophy, if we lock up juries for them to make a decision, then we should lock up the judge to make his decision too.
>
> I intend to start working on the case right away, and I hope probably by the latter part of this next week, to let you know what the decision is.

Judge Conti, in effect, followed the philosophy of the Federal Circuit Chief Judge Markey:

> Decide from the bench. You are never going to be in a better position to decide the case than you are at the end of trial. . . . The sequence is: (1) read the material, (2) hear the evidence, (3) record your daily impressions, (4) hear the closing arguments, and (5) decide from the bench. You will do what's appropriate in due course in the way of findings and conclusions.

Markey, H.T., Some Patent Problems, 80 F.R.D. 203, 218 (1979). Rather than commending Judge Conti for his conscientiousness, the Federal Circuit picked apart his decision and chastised him for his efficiency. No wonder Judge Conti recused himself in this case on remand (Appx. E, A58).

IV

THE FEDERAL CIRCUIT'S CRITICISM OF THE TRIAL COURT'S ANALYSIS OF OBVIOUSNESS WAS LEGALLY MISPLACED

The Constitution granted certain powers to Congress, among them the power—if it chose to use it—to grant an "exclusive right" to inventors for limited times.[13]

Originally, pursuant to the 1790 Act and the 1793 Patent Act,[14] patents were granted to anyone who fulfilled certain procedural requirements. P.J. Federico, *Commentary on the New Patent Act*, 35 USCA 1, 4 (1983).[15] There were no substantive requirements until 1836 when Congress created a Patent Office with the power to examine and refuse patent applications for attempting to claim unpatentable subject matter.[16]

Prior to the most recent revision in 1952, there existed two statutory conditions of patentability, utility and novelty, as defined in the patent statute, 35 U.S.C. §§ 101-102.[17]

One of the major changes in the 1952 Act consisted of codifying a third condition for patentability, which had existed in the case law for over 100 years since this Court's opinion in *Hotchkiss v. Greenwood*, 52 U.S. 248 (1851). This third condi-

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[13] Specifically, the U.S. Constitution provides:
The Congress shall have power . . . To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries. Art. I, § 8, Cl. 8.

[14] April 10, 1790 [c.7, 1 Stat. 109]; February 21, 1793 [c.11, 1 Stat.] 318, respectively.

[15] Mr. Federico, then Examiner-in-Chief of the U.S. Patent Office, was the principal drafter of the 1952 patent statute. His commentary relating thereto was published at 35 USCA 1-70.

[16] Enacted July 4, 1836 [c. 357, 5 Stat. 117].

[17] Section 31 of former title 35, USCA; R.S. 4886.

tion was entitled "non-obviousness" and was assigned to § 103.[18] *Graham*, 383 U.S. at 14.

In *Hotchkiss*, John G. Hotchkiss invented a new doorknob in which the handle was made out of either clay or porcelain. Prior doorknob handles had only been made out of either wood or metal.

This Court approved a jury instruction to the effect that if the substitution of a knob of porcelain for wood or metal in a doorknob assembly required no more skill or ingenuity to construct than that possessed by an ordinary mechanic acquainted with the business, then Hotchkiss was not entitled to a patent.

The codification of *Hotchkiss* has been acknowledged:

> Section 103, for the first time in our statute, provides a condition which exists in the law and has existed for more than 100 years, but only by reason of decisions of the courts. An invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent.

Graham, 383 U.S. at 14.

As set out, *infra*, the Federal Circuit was legally incorrect in finding error in the trial court's application of § 103.

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[18] Specifically, the relevant portion of § 103 states:
A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

A. The Federal Circuit's Criticism Of The Trial Court's Looking to "Substitution" Of An Improved Material in Evaluating Obviousness Is Legally Inconsistent With Supreme Court Precedents

The trial court found the difference between the David invention and the common, previously used, sandwich assays was that David substituted monoclonals for polyclonals as the reagents. The determination of differences between the prior art and the claimed invention is one of the three fact-finding steps mandated by this Court in applying § 103. *Graham,* 383 U.S. at 15. As explained, *supra,* prior commercial sandwich assays employed polyclonals, rather than monoclonals, because technology was not available for mass producing monoclonals as would be required for commercial exploitation (A36,48). That all changed when Kohler and Milstein developed such a process. Once available, it was simply a matter of time and money until the appropriate monoclonals were identified, produced and substituted for polyclonals.

This evidence of record led the trial court to hold:

> [I]t would be obvious to substitute in a known sandwich assay, known high affinity monoclonal antibodies for polyclonal antibodies of similar affinity for the known advantages of monoclonal antibodies over polyclonal antibodies in immunoassays. [A45]

The Federal Circuit somehow found fault with this approach *as a matter of law*, stating:

> Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. [A28]

The Federal Circuit's criticism of the trial court's evaluation of the patented invention as based on a substitution of elements is inconsistent with this Court's precedents. The trial court is no more at fault than this Court in *Graham:*

> This court formulated a general condition of patentability in 1851 in *Hotchkiss v. Greenwood* . . . . The patent involved a mere *substitution* of materials—porcelain or clay for wood or metal in doorknobs—and the Court condemned it. [Emphasis added.]

383 U.S. at 11.[19]

Contrary to the Federal Circuit's holding, *Hotchkiss* was codified in the 1952 statute, § 103, iterated in this Court's decision in *Graham*, 383 U.S. at 17, and is, after 130 years, still in force today.

Such a blatant dichotomy in the law, between Supreme Court and Federal Circuit approaches to § 103, presents the type of question of importance requiring guidance to both trial courts and

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[19] In *Hotchkiss*, the patentability of an improved doorknob based on the substitution of an improved material was analyzed as follows (we have inserted elements analogous to our case [in brackets] where appropriate):

> But in the case before us, the knob [polyclonals] is not new . . . nor the means by which the metallic shank is securely fastened [the sandwich assay] therein. All these were well known, and in common use; and the only thing new is the substitution of a knob of a different material [monoclonals] from that heretofor used [polyclonals] in connection with this arrangement [sandwich assay].
>
> Now it may very well be, that, by connecting the clay or porcelain knob [monoclonals] with the metallic shank in this well-known mode [sandwich assay], an article is produced better and cheaper [has a higher sensitivity] than in the case of the metallic or wood knob [polyclonal]; but this does not result from any new mechanical device or contrivance, but from the fact, that the material of which the knob is composed [monoclonals] happens to be better adapted to the purpose for which it is made. The improvement consists in the superiority in the material [monoclonals], and which is not new, over that previously employed in making the knob [polyclonals].
>
> *But this, of itself, can never be the subject of a patent.* [Emphasis added.]
>
> *Hotchkiss*, 52 U.S. at 265-66.

litigants alike. The judicial system fails when trial courts are reversed for following Supreme Court precedent.

B. "Obvious To Try"—A Proper Factual Inquiry in Determining Patentability

In evaluating the patentability of Hybritech's monoclonal sandwich assay it is not enough to find that it was an improvement over a polyclonal sandwich assay because it was better or cheaper. Such a test was rejected by this Court in *Hotchkiss*, 52 U.S. at 256-66, and *Graham*, 383 U.S. at 11. It is necessary to evaluate whether the invention resulting from the specific substitution would have been obvious to one of ordinary skill in the relevant art.

One starting point is to determine whether there was some suggestion or teaching in the prior art to substitute monoclonal antibodies for polyclonal antibodies in a sandwich assay. *Panduit*, Slip. op. at 11 ("elements of separate prior patents cannot be combined when there is no suggestion of such combination anywhere in those patents . . .") *W. L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983), *cert. den.*, 469 U.S. 851 (1984).

In *Application of Antle*, the CCPA, a predecessor of the Federal Circuit, suggested a picturesque approach. Imagine "the inventor working in his shop with the prior art references—which he is presumed to know—hanging on the walls around him." 444 F.2d 1168, 1171 (CCPA 1971).[20] The ultimate test being, would it have been obvious to him to pick and substitute the elements to achieve the result sought to be patented?

The Federal Circuit has suggested how the analysis should be made. First, determine if the prior art references are sufficiently

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[20] *Application of Antle* was overruled by *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1452 (Fed. Cir. 1984) insofar as it focused on the *inventor* being presumed to have knowledge of the relevant prior art. Rather, the presumption is directed to the hypothetical person of ordinary skill in the art referred to in § 103. *Application of Antle* is still an appropriate visualization directed to the hypothetical person at his workbench.

related so that the hypothetical person, referred to in § 103, can be charged with knowing them.

That being so, the next questions are:

> (a) Whether a combination of the teachings of all or any of the references have suggested (expressly or by implication) the possibility of achieving further improvement by combining such teachings along the line of the invention in suit, and
>
> (b) Whether the claimed invention achieved more than a combination which any or all of the prior art references suggested, expressly or by reasonable implication.

In re Sernaker, 702 F.2d 989, 994 (Fed. Cir. 1983).

In this case, the prior art disclosed a sandwich assay in which, out of necessity, polyclonal antibodies had been used as reagents. Yet, once Kohler and Milstein developed the technology for mass producing monoclonal antibodies, excitement grew. Persons in the immunoassay field began suggesting, in publications, the benefits of substituting monoclonal antibodies for polyclonal antibodies in the existing immunoassays, including the sandwich assay (A43, 44).

The trial court made specific reference in its opinion to the prior art publications which taught the use of monoclonal antibodies in competitive assays, in sandwich assays, and which predicted the use of monoclonal antibodies in immunoassays, generally (A50-52).

The trial court found that evidence persuasive holding:

> The testing kits and procedures prior to Kohler and Milstein used polyclonal antibodies, and once Kohler and Milstein invented the technology for developing monoclonal antibodies, it was obvious to use monoclonal antibodies in a sandwich assay where polyclonal antibodies had been used in the past. [A47]

But the Federal Circuit has developed a procedure for reversing a trial court's holding of invalidity even when the prior art suggested the particular invention. In order to do so, the Federal Circuit has labelled the evidence which suggests the claimed

invention as "obvious to try" evidence. The Federal Circuit continues by assuming evidence it chooses to label as "obvious to try" evidence is automatically of *no weight* in determining patentability.

Nothing in the Federal Circuit opinion suggested the trial court was not in a superior position to evaluate the "obvious to try" evidence in determining patentability. In any event, contrary to the Federal Circuit's implications, the trial court never mentioned the "obvious to try" label. Yet, by way of this labelling tactic the Federal Circuit has allowed itself to reach opposite results based on the identical analysis of prior art evidence suggesting the patented invention, depending on whether it wants to affirm or reverse.

The trial court, consistent with Federal Circuit precedents, properly evaluated whether the substitution of monoclonals for polyclonals was suggested by the prior art in ultimately determining obviousness. The Federal Circuit's reprimand for employing a legal standard *neither mentioned nor employed* by the trial court is legally without basis. Such a meaningless slogan-type standard employed simply to justify a reversal of the trial court can only increase frustration on the part of litigants and trial court judges as evidenced by Judge Conti's recusal.

V

THE APPROPRIATE REMEDY WHEN THE APPELLATE COURT DEEMS FINDINGS OF FACT EITHER INADEQUATE OR YET TO BE DECIDED IS TO REMAND FOR FURTHER PROCEEDINGS

As discussed, *supra,* Rule 52(a) governs the scope of the appellate function by allowing courts to set aside clearly erroneous fact findings. Yet, while the appellate court may set aside fact findings, *it is not empowered to substitute its own fact findings for those it holds inadequate.*

When findings, as in this case, are held inadequate, the appellate court should remand and instruct the trial court to "find the facts specially and state separately its conclusions of law thereon."

Pentec, Inc. v. Graphic Controls Corp., 776 F.2d 309, 318 (Fed. Cir. 1985) (Harvey, concurring). A remand would effectively promote the intent of Rule 52(a) in two specific ways:

> First, it would ensure proper consideration of a case by a District Court. Second, it would leave intact the clearly erroneous standard of review; a standard which appears to have undermined *sub silencio* in some cases on appeal in an effort by the Courts of Appeal to compensate for inadequate consideration by a District Court.

Pentec, 776 F.2d at 319.

This case is also inconsistent with another Federal Circuit case, *Custom Accessories, Inc. v. Jeffrey-Allen Industries, Inc.*, No. 85-2728, slip op. at 19 (Fed. Cir. Dec. 12, 1986), which held in a situation where there are inadequate findings by the district court "we *must remand* to allow the district court to do so." (Emphasis added.)

As support for its statement that it unequivocally *must remand* to allow the trial court to act as the trier of fact, the Federal Circuit relied on this Court's decision in *Icicle Seafoods*, citing the following section:

> If the Court of Appeals believed that the District Court had failed to make findings of fact essential to a proper resolution of the legal question, it should have remanded to the District Court to make those findings. If it was of the view that the findings of the District Court were "clearly erroneous" within the meaning of Rule 52(a), it could have set them aside on that basis. If it believed that the District Court's factual findings were unassailable, but that the proper rule of law was misapplied to those findings, it could have reversed the District Court's judgment. *But it should not simply have made factual findings on its own.* [Emphasis added.]

106 S.Ct. at 1530; See also *Jones v. Hardy*, 727 F.2d 1524, 1534 (Fed. Cir. 1984). (Kashiwa, J., dissenting from majority's decision not to remand for findings)

Furthermore, the appellate court should not make fact findings where none existed below. *Pullman-Standard v. Swint*, 456 U.S.

273, 291-92 (1982) ("When an appellate court discerns that a district court has failed to make a finding because of an erroneous view of the law, the usual rule is that there should be a remand for further proceedings to permit the trial court to make the missing findings: 'Fact finding is the basic responsibility of district courts, rather than appellate courts, and . . . the Court of Appeals Should not have resolved in the first instance this factual dispute which had not been considered by the District Court.' ")

In this case, the trial court found "no credible evidence of conception (of the invention) prior to May of 1980." (A46) Yet, the Federal Circuit reversed the trial court decision finding David and Greene conceived the claimed invention in January 1979 (A19). But, in order for Hybritech to rely on its conception date as its date of invention, it must have established diligence between the date of conception and the date it reduced the invention to practice (A15, 19). 35 U.S.C. § 102(g).

The Federal Circuit made a finding of fact as to *diligence* based primarily on the testimony of witnesses, not listed as credible by the trial court. This issue intentionally *was not addressed by the trial court* because it was unnecessary in view of its holding on lack of conception.

The Federal Circuit's action is a far cry from the spirit of Rule 52(a), and is inconsistent with a litigant's right to have the *trier of fact*, i.e., the trial court, decide, at least in the first instance, all disputed factual issues. In fact, the Federal Circuit made twelve specific references to witness testimony in support of its *de novo* findings of conception and diligence (A16-19).

The Federal Circuit's action is further troubling in light of its inconsistency in remanding the issue of patent infringement (A32) but not remanding the issue of diligence. While both issues were argued to the trial court, and neither were addressed, the Federal Circuit ruled on one issue and remanded the other.

The Federal Circuit's creation of fact findings, on issues it found either inadequately addressed or not addressed, is legally inappropriate. Such a cavalier ignoring of Rule 52(a) demonstrates the importance of granting MAB's Petition, thereby reminding the Federal Circuit of the scope of its appellate function.

VI

CONCLUSION

The Federal Circuit disregarded Rule 52(a) and the deference iterated in *Anderson* to which a trial court's credibility evaluations of the evidence are entitled and rewrote the history of Hybritech's invention in order to reverse the trial court.

In its first case dealing with how the statutory conditions of patentability relate to this most important area of biotechnology, the Federal Circuit has granted a monopoly to Hybritech which will affect research and development in the diagnostic test kit industry for years to come. But, more importantly, the Federal Circuit has taken away from the public domain an invention which the trial court found was invalid on five statutory bases and had been previously invented by others.

That disregard of Rule 52 has made the trial court experience meaningless; rendering those proceedings a fact-gathering exercise for an appellate *de novo* review.

Moreover, this Court should grant Certiorari because the Federal Circuit in applying the obviousness standard of patentability has ignored this Court's precedents in *Hotchkiss* and *Graham*. The consistency with which the obviousness statutory condition of patentability should be applied has been further confused by the Federal Circuit's intentional use of separate labels for an identical inquiry depending on its desired outcome on the merits.

As stated in the opening words of *Graham*, decided in 1966:

> After a lapse of 15 years, the Court again focuses its attention on the patentability [obviousness] of inventions.

383 U.S. at 3.

In light of the recent creation of the Federal Circuit in 1982, with exclusive appellate jurisdiction of all appeals relating to patents, the time is ripe for this Court to once again delve into the Constitutional standards of patentability.

Finally, Certiorari is warranted because the Federal Circuit acted directly contrary to this Court's decision in *Icicle Seafoods*,

which held an appellate court should remand those factual findings deemed inadequate. The Federal Circuit not only substituted its own factual findings for those it found inadequate, but contrary to *Pullman-Standard*, also made *de novo* findings on disputed issues not addressed by the trial court.

Dated: February 4, 1987

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Appendix A

United States Court of Appeals
for the Federal Circuit

Appeal No. 86-531

Hybritech Incorporated,

Appellant,

v.

Monoclonal Antibodies, Inc.,

Appellee.

Decided: September 19, 1986

Before RICH, DAVIS and SMITH, Circuit Judges.

RICH, Circuit Judge.

This appeal is from the August 28, 1985, decision of the United States District Court for the Northern District of California, 623 F. Supp. 1344, 227 USPQ 215, in favor of defendant Monoclonal Antibodies, Inc. (Monoclonal) holding that all 29 claims of plaintiff's patent No. 4,376,110 entitled "Immunometric Assays Using Monoclonal Antibodies" ('110 patent), issued to Dr. Gary S. David and Howard E. Greene and assigned to Hybritech Incorporated (Hybritech), are invalid as anticipated under 35 USC 102(g), for obviousness under § 103, and under § 112 first and second paragraphs. We reverse and remand.

Background

Vertebrates defend themselves against invasion by microorganisms by producing antibodies, proteins which can complex with the invading microorganisms and target them for destruction or removal. In fact, any foreign molecule of sufficient size can act as a stimulus for antibody production. Such foreign molecules, or antigens, bear particular sites or epitopes that represent antibody recognition sites. B cell lymphocytes, the cells that actually produce antibodies, recognize and respond to an epitope on an antigen by reproducing or cloning themselves and then producing

antibodies specific to that epitope. Even if the antigen is highly purified, the lymphocytes will produce antibodies specific to different epitopes on the antigen and so produce antibodies with different specificities. Furthermore, because the body is exposed to many different antigens, the blood of a vertebrate will contain antibodies to many different antigenic substances.

Scientists and clinicians have long employed the ability of antibodies to recognize and complex with antigens as a tool to identify or label particular cells or molecules and to separate them from a mixture. Their source of antibodies has been primarily the serum separated from the blood of a vertebrate immunized or exposed to the antigen. Serum, however, contains a mixture of antibodies directed to numerous antigens and to any number of epitopes on a particular antigen. Because such a mixture of antibodies arises from many different clones of lymphocytes, it is called "polyclonal."

Recent technological advances have made it possible to isolate and cultivate a single clone of lymphocytes to obtain a virtually unlimited supply of antibodies specific to one particular epitope. These antibodies, known as "monoclonal antibodies" because they arise from a single clone of lymphocytes, are produced by a relatively new technology known as the hybridoma. Hybridomas are produced by fusing a particular cancer cell, the myeloma cell, with spleen cells from a mouse that has been injected or immunized with the antigen. These fusions are isolated by transferring them to a growth fluid that kills off the unfused cancer cells, the unfused spleen cells dying off by themselves. The fused hybrid spleen and myeloma cells, called hybridomas, produce antibodies to the antigen initially injected into the mouse. The growth fluid containing the hybridomas is then diluted and put into individual test tubes or wells so that there is only one hybridoma per tube or well. Each hybridoma then reproduces itself and these identical hybridomas each produce identical monoclonal antibodies having the same affinity and specificity. In this way, a virtually unlimited supply of identical antibodies is created, directed to only one epitope on an antigen rather than, as with polyclonal antibodies, to many different epitopes on many different antigens.

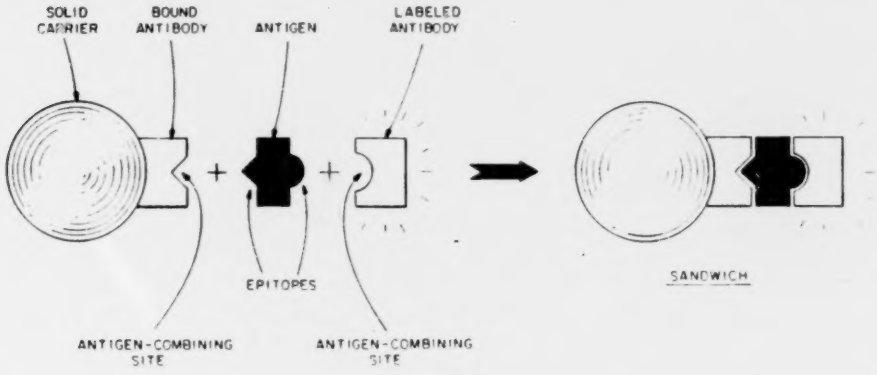
In addition to the specificity of antibodies to particular epitopes discussed above, antibodies also have a characteristic "sensitivity," the ability to detect and react to antigens. Sensitivity is expressed in terms of "affinity:" the greater an antibody's ability to bind with a particular antigen, the greater the antibody's affinity. The strength of that antibody-antigen bond is in part dependent upon the antibody's "affinity constant," expressed in liters per mole, for the antigen.

Immunoassays, the subject matter of the '110 patent, are diagnostic methods for determining the presence or amount of antigen in body fluids such as blood or urine by employing the ability of an antibody to recognize and bind to an antigen. Generally, the extent to which the antibody binds to the antigen to be quantitated is an indication of the amount of antigen present in the fluid. Labelling the antibody or, in some cases, the antigen, with either a radioactive substance, I^{125}, or an enzyme makes possible the detection of the antibody-antigen complex. In an extreme case, where the fluid sample contains a very low level of the antigen, binding might not occur unless the antibodies selected or "screened" for the procedure are highly sensitive.

In the case of a "competitive" immunoassay, a labelled antigen reagent is bound to a limited and known quantity of antibody reagent. After that reaction reaches equilibrium, the antigen to be detected is added to the mixture and competes with the labelled antigen for the limited number of antibody binding sites. The amount of labelled antigen reagent displaced, if any, in this second reaction indicates the quantity of the antigen to be detected present in the fluid sample. All of the antigen attached to the antibody will be labelled antigen if there is no antigen in the test fluid sample. The advantage of this method is that only a small amount of antibody is needed, its drawback, generally, that the system must reach equilibrium, and thus produces results slowly.

In the case of a "sandwich" assay, otherwise known as an immunometric assay, the latter being a term coined by Dr. Lawton Miles in 1971, a quantity of unlabelled antibody reagent is bound to a solid support surface such as the inside wall of a test tube containing a complex of the fluid sample containing the

antigen to be detected and a labelled *antibody* reagent. The result is an insoluble three part complex referred to as a sandwich having antibody bread and antigen filling. This figure is illustrative of the sandwich concept:



The advantage of the sandwich assay is that it is fast and simple, its drawback that enormous quantities of antibodies are needed.

Hybritech

Hybritech, started in 1978 and joined thereafter by coinventors Green and Dr. David, has, since 1979, been in the business of developing diagnostic kits employing monoclonal antibodies that detect numerous antigens and thus a broad range of conditions such as pregnancy, cancer, growth hormone deficiency, or hepatitis. Examples of antigens include influenza viruses, immunoglobin E (IgE) which indicates allergic reaction, human chorionic gonadotropin (HCG) which indicates pregnancy, and prostatic acid phosphatase (PAP) which indicates prostate cancer, to name a few. Dr. Adams, a business-experienced scientist, joined the company in May 1980 as head of research and development. The '110 patent, application for which was filed August 4, 1980, issued March 8, 1983, with claims defining a variety of sandwich assays using monoclonal antibodies. Claim 19, apparently the broadest of the twenty-nine in the patent, is directed generally to a sandwich assay and reads (emphasis ours):

19. *In an immunometric assay* to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, *the improvement comprising* employing monoclonal antibodies having an affinity for the anitgenic substance of at least about 10^8 liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.

Claim 1, directed particularly to a reverse sandwich assay, explained infra, reads:

1. A process for the determination of the presence of [sic, or] concentration of an antigenic substance in a fluid comprising the steps:

(a) contacting a sample of the fluid with a measured amount of a soluble first monoclonal antibody to the antigenic substance in order to form a soluble complex of the antibody and antigenic substance present in said sample, said first monoclonal antibody being labelled;

(b) contacting the soluble complex with a second monoclonal antibody to the antigenic substance, said second monoclonal antibody being bound to a solid carrier, said solid carrier being insoluble in said fluid, in order to form an insoluble complex of said first monoclonal antibody, said antigenic substance and said second monoclonal antibody bound to said solid carrier;

(c) separating said solid carrier from the fluid sample and unreacted labelled antibody;

(d) measuring either the amount of labelled antibody associated with the solid carrier or the amount of unreacted labelled antibody; and

(e) relating the amount of labelled antibody measured with the amount of labelled antibody measured for a control sample prepared in accordance with steps (a)-(d), said control sample being known to be free of said antigenic substance, to determine the presence of antigenic substance in said fluid sample, or relating the amount of labelled antibody measured with the amount of labelled antibody measured for samples containing known amounts of antigenic substance prepared in accordance with steps (a)-(d) to determine the concentration of antigenic substance in said fluid sample, the first and second monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole.

The District Court Decision

Hybritech sued Monoclonal March 2, 1984, for damages and an injunction alleging that the manufacture and sale of Monoclonal's diagnostic kits infringed the '110 patent. Trial without a jury began on August 5, 1985, and concluded August 23, 1985, thirty witnesses having been heard and over 2,000 pages of transcript generated. The district court produced the reported opinion, findings, and conclusions, which use nearly verbatim Monoclonal's *pre-trial* brief and *pre-trial proposed* findings of fact and conclusions of law, in three days in support of the judgment now on appeal.

The district court held that the claimed subject matter of the '110 patent was neither conceived nor actually reduced to practice before May 1980, and was anticipated under § 102(g) by the actual reduction to practice of the invention by Drs. Uotila and Ruoslahti at the La Jolla Cancer Research Foundation (LJCRF) as early as November of 1979 and by the actual reduction to practice of the invention by Drs. Oi and Herzenberg (Oi/Herzenberg work) at the Stanford University Laboratory as early as July 1978, later published in December of 1979.

The district court also held the claims of the '110 patent invalid for obviousness from the Oi/Herzenberg work in view of (1) a February 1979 article by M. E. Frankel and W. Gerhard (Frankel article) which discloses high-affinity monoclonal antibodies, and

apparently in view of numerous other references including (2) the work of Nobel Prize winners G. Kohler and C. Milstein disclosing a Nobel Prize-worthy method for producing monoclonal antibodies in vitro (outside the body) published in an August 7, 1975, article; (3) U.S. Patent No. 4,244,940 issued to Jeong et al. disclosing a simultaneous polyclonal assay (Jeong), U.S. Patent No. 4,098,876 to Piasio et al. disclosing a reverse polyclonal sandwich assay (Piasio), U.S. Patent No. 4,016,143 to Schurrs et al. disclosing a forward polyclonal sandwich assay (Schurrs); (4) a July 1979 publication by A. C. Cuello et al. disclosing the use of monoclonal antibodies in competitive assays; and (5) eight articles dated between January 1979 and March 6, 1980, "predicting" that monoclonal antibodies would be used in future immunoassays.[1]

The district court also invalidated the patent on various grounds based on 35 USC 112, first and second paragraphs, as hereinafter discussed.

A. The References

1. *Kohler and Milstein's Nobel Prize-Winning Work: Producing Monoclonal Antibodies In Vitro For the First Time*

In early immunoassay work, polyclonal antibodies produced in vivo (in the body) in mice were used to bind with the antigen to be detected in the body fluid sample. Mice were immunized by injection with antigen so that the lymphocytes in their bodies produced antibodies that attacked the injected antigen. Those polyclonal antibodies were withdrawn from the animal's blood and used in immunoassays. The major problem was that when the mice's immune systems changed or the mice died, the antibodies changed or died too; supply was limited and uncertain.

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[1] With respect to obviousness, one portion of the district court's opinion apparently relies on all of the above listed references, (1)-(5), for the obviousness holding while a later portion entitled "CONCLUSIONS OF LAW" relies on only the Oi/Herzenberg and Frankel articles. Furthermore, the district court did not state that the LJCRF work was considered for purposes of § 103, although we recognize that § 102(g) prior art can be used for § 103.

As the examiner was aware, Kohler and Milstein developed a technique not only for producing antibodies in vitro, independent of a living body, thus eliminating dependence on a particular animal, but for in vitro production of monoclonal antibodies by hybridomas, discussed in the Background section, supra.

Given that sandwich assays require enormous amounts of antibodies, companies like appellant and appellee, which utilize monoclonal antibodies for sandwich assays, would not be in business were it not for the work of Kohler and Milstein.

2. *The Work of Drs. Ruoslahti, Uotila, and Engvall at the La Jolla Cancer Research Foundation (LJCRF) in 1979 and 1980*

Dr. Ruoslahti performed mostly competitive immunoassays using polyclonal antibodies to alphafetoprotein (AFP) antigens at the City of Hope since 1970. Dr. Uotila joined him in late 1978 to perform immunoassays using monoclonal antibodies to AFP. After producing monoclonal antibodies to AFP and performing competitive radio immunoassays (RIA—a competitive assay that uses a radioactive label) with monoclonal antibodies at the City of Hope in mid-1979, Drs. Ruoslahti, Uotila and Engvall left LJCRF.

In the fall of 1979, September or October according to Dr. Uotila, discussion and work began on using monoclonal antibodies to AFP in a sandwich assay. Dr. Uotila, the principal researcher in this particular endeavor, generated six notebooks while at the City of Hope and LJCRF. The next-to-last page of notebook four contained a note to Dr. Uotila from Dr. Ruoslahti reading:

> Sometime you should enzyme label a good monoclonal antibody so that you can set up a sandwich assay. If you use two monoclonal antibodies, you may be able to do the assay with a single incubation, since the monoclonal antibodies are likely to be directed against different determinants and not compete with one another.

Although Dr. Uotila's notebook pages were, for the most part, unsigned, undated, and uncorroborated, Dr. Ruoslahti's testimony, placed the date of this note at about October 1979 by

referring to the first pages of notebook five which were dated in early November 1979. Dr. Ruoslahti testified that one curve on one graph on page 43D of notebook five showed a successful simultaneous sandwich assay using monoclonal antibodies about November 5, 1979, although no data supporting that graph could be found elsewhere in the notebook. He further testified that the affinity of the monoclonal antibodies used for that test was not calculated until 1980 but that the raw data necessary for that calculation was generated in 1979.

Dr. Uotila stated in her deposition (she did not testify at trial) that she started work on a sandwich assay using monoclonal antibodies between October 4 and the end of that month, 1979, and that she could not remember the procedure used nor was there enough information in her notebook, including page 43D, to refresh her memory. She did remember, although she continued work on this assay because the tests did not yield repeatedly good curves without which she would not publish her work, that the assay on page 43D was successful. Dr. Engvall testified about a discussion of Dr. Uotila's monoclonal antibody work with her while at the City of Hope and about first performing a sandwich assay after arriving at LJCRF in 1979.

3. *The Work of Drs. Oi and Herzenberg at the Stanford University Laboratory in 1978 Published in December 1979*

Drs. Oi and Herzenberg used monoclonal antibodies to "map" epitopes or determine the number and location of different antibody binding sites on a known quantity of IgE antigen by attaching to it an antibody bound to a carrier and exposing that antigen to other monoclonal antibodies. The antibodies either attached to epitopes on the antigen or were blocked from doing so by the other monoclonal antibodies, depending on the location and number of epitopes; if the epitopes on the antigen were too close together and the number of antibodies too great, few antibodies would bind to the antigen. Hybritech points out that both Dr. Herzenberg and Dr. Oi testified that *their work did not involve determining the presence or quantity of antigen*, that they had no idea what the affinities of the monoclonal antibodies used were, and that those values were never calculated.

One unsigned, unwitnessed page from three large laboratory notebooks, which Hybritech argues is insufficient because it does not identify the chemical reagents or protocol used, was relied on by Monoclonal to establish actual reduction to practice of the Oi/Herzenberg work in 1978 to establish a case of § 102(g) prior invention by another. The district court agreed with Monoclonal that the Oi/Herzenberg work anticipated the claimed invention and, in addition, combined this work with the Frankel publication to hold that the claimed subject matter was obvious under § 103.

4. *The Frankel Article: Monoclonal Antibodies Having Affinities of 10^9 liters/mole*

Frankel describes an RIA (radioimmunoassay) method for the rapid determination of affinity constants for monoclonal antibodies produced from hybridomas. The article states that the assay used is applicable only to antibodies with binding constants of about 10^{10}liters/mole and discloses the binding constants for antibodies to several closely related strains of influenza virus.

The district court found that Frankel disclosed monoclonal antibodies having the affinity constants claimed in the '110 patent, 10^8 to over 10^9 liters/mole.

5. *The Cuello Article and the Jeong, Piasio, and Schurr Patents Considered by the Examiner*

Cuello, dated July 1979, states that it describes the usefulness of monoclonal antibodies in the characterization and localization of neurotransmitters such as Substance P, a peptide clearly associated with the transmission of primary sensory information in the spinal cord. The article discloses producing monoclonal antibodies from hybrid myelomas (hybridomas), their use in conventional radioimmunoassay techniques, and the benefits from doing so which flow from the ability to derive permanent cell lines capable of continuous production of highly specific antibodies.

The district court found that the examiner twice rejected all of the claims of the '110 patent based on Cuello alone or in combination with the Jeong, Piasio, and Schurr references which disclose various sandwich assays using polyclonal antibodies. The court also found that the examiner allowed the claims after they

were amended to include the 10^8 affinity limitation and after Richard Bartholomew, a Hybritech employee, submitted an affidavit alleging the advantages of using monoclonal rather than polyclonal antibodies in sandwich assays.

Apparently based on the testimony of Monoclonal's expert witness Judith Blakemore, a named inventor of the Jeong patent, manager of antibody programs at Bio-Rad Laboratories from 1975 to 1982, and currently manager of monoclonal antibody therapeutics at Cetus Corporation, a Hybritech competitor in immunoassay diagnostics, the district court stated that the "reasons for allowance were not well-founded because (1) the alleged advantages were expected as naturally flowing from the well-known natural characteristics of monoclonal antibodies . . . ; (2) . . . were not significant . . . ; or (3) were at best minor," although they were "argued to the examiner as if they were" important. These were Monoclonal's words from its pretrial submission adopted by the court.

6. *The References That "Predicted" the Use of Monoclonal Antibodies in Immunoassays*

The district court stated, again in Monoclonal's words, that "it is of the utmost importance" that the advantages of monoclonal antibodies were "predicted by a number of authorities," eight to be exact, not important enough to list here, after the Kohler and Milstein discovery and after monoclonal antibodies became available.

B. *The Claimed Subject Matter of the '110 Patent*

Hybritech argues that the district court's determination that there is no credible evidence of conception or reduction to practice of the '110 invention before May 1980 is error because Dr. David's laboratory notebooks, Nos. 21 and 24, clearly show successful sandwich assays using monoclonal antibodies in August, September, and October of 1979. At the least, argues Hybritech, the invention was conceived in January of 1979, long before Drs. Ruoslahti, Engvall, and Uotila began work on a sandwich assay using monoclonal antibodies, and diligence was thereafter exercised until constructive reduction to practice oc-

curred by the filing of the '110 patent application on August 4, 1980.

Dr. David and Greene testified that pages 2118 to 2122 of Dr. David's notebook, dated January 4, 1979, and witnessed January 30, 1979, disclose the generic conception of the invention in the context of the physical support structure used to carry out a sandwich assay, and Dr. David testified on redirect that (1) Page 1128 of notebook 21, dated May 27, 1979, recorded an early attempt at a sandwich assay that failed, (2) on August 3, 1979, as recorded at page 1166, a sandwich assay using monoclonal antibody 068 attached to a solid carrier, a radio-labelled 068 antibody, and a hepatitis antigen from an Abbott Labs polyclonal competitive assay kit was successfully performed, and (3) a sandwich assay using a bound 259 antibody, a radio-labelled 068 antibody, and a hepatitis antigen was successfully performed on September 21, 1979. Hybritech also urges that work in October 1979 directed to determining whether certain monoclonal antibodies were recognizing the same or different determinants, was a reduction to practice.

Monoclonal points out that these notebook pages do not expressly state that monoclonal antibodies of 10^{8} liters/mole affinity were used in a sandwich assay and that the May, August, and September notebook entries were not witnessed until about the time Dr. Adams, experienced in patent matters, joined Hybritech and advised its researchers on properly recording laboratory work. They therefore claim that actual reduction to practice was not shown before May 1980.

OPINION

1. *Review Under Rule 52(a) Fed. R. Civ. P.*

Rule 52(a) "ensures care in the preparation of an opinion . . . and provides appellate courts with the benefit of the District Court's insights into a case," *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 318, 227 USPQ 766, 772 (Fed. Cir. 1985) (Harvey, Senior District Judge, concurring) by requiring a district court to "find the facts specially and state separately its conclusions of law thereon." With the exception of the first eight

paragraphs, the first half of the district court's opinion here is Monoclonal's *pretrial* brief and the last three pages of the opinion are Monoclonal's *pretrial* findings of fact and conclusions of law. The district court adopted the above documents virtually verbatim, with the exception of portions of each concerning inequitable conduct and noninfringement, apparently without inviting a response from Hybritech, resulting in a repetitious (as the district court admitted in the opinion), sometimes internally inconsistent, and hard to follow opinion that presents us with a difficult task in gleaning the basis for many of the conclusions. For some of the findings, submitted before trial, no supporting evidence was introduced at trial.

The Supreme Court, in *Anderson v. City of Bessemer City, N.C.*, 105 S. Ct. 1504 (1985), strongly criticized the practice of "verbatim adoption of findings of fact prepared by prevailing parties, particularly when those findings have taken the form of conclusory statements unsupported by citation to the record." *Anderson*, supra at 1511. This court also has cautioned against the adoption of findings, especially when proposed by a party before trial, as here, and stated that the likelihood of clear error in those findings increases in such a situation. *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1457, 221 USPQ, 481, 485 (Fed Cir. 1984). Notwithstanding our misgivings about whether the findings in this case, prepared before any evidence was introduced, satisfy the objectives of Rule 52(a)—a carefully prepared opinion providing the reviewing court with the benefit of the district court's *reasoned insights* into the case—those findings are the district court's and may be reversed only if clearly erroneous. *See Anderson*, supra, at 1511; *Lindemann*, 730 F.2d at 1457, 221 USPQ at 485.

"A finding is clearly erroneous when, although there is evidence to support it, the reviewing court on the entire evidence is left with the definite and firm conviction that a mistake has been committed." *United States v. United States Gypsum Co.*, 333 U.S. 364, 395 (1948). "This standard plainly does not entitle a reviewing court to reverse the finding of the trier of fact simply because it is convinced that it would have decided the case differently." *Anderson*, supra, at 1511. In other words, "if the

district court's account of the evidence is plausible in light of the record viewed in its entirety" or "where there are two permissible views of the evidence," the factfinder cannot be clearly erroneous. *Anderson*, supra, at 1511 (quoting *United States v. Yellow Cab Co.*, 338 U.S. 338, 342 (1949)). This is so, stated the Court in dictum, *see Anderson*, supra, at 1516 (Blackmun, J., concurring), even when the district court's findings rest on physical or documentary evidence or inferences from other facts and not on credibility determinations. *See also* Rule 52(a) Fed. R. Civ. P. (as amended Aug. 1, 1985). If the latter are involved, "Rule 52 demands even greater deference to the trial court's findings" but a trial judge may not "insulate his findings from review by denominating them credibility determinations"; if documents or objective evidence contradict the witness's story, clear error may be found even in a finding purportedly based on a credibility determination. *Anderson*, supra, at 1512-13. We proceed in light of all these principles.

II. *Presumption of Validity*

Under 35 USC 282, a patent is presumed valid, and the one attacking validity has the burden of proving invalidity by clear and convincing evidence. *See, e.g., American Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1360, 220 USPQ 763, 770 (Fed. Cir. 1984). Notwithstanding that the introduction of prior art not before the examiner may facilitate the challenger's meeting the burden of proof on invalidity, the presumption remains intact and on the challenger throughout the litigation, and the clear and convincing standard does not change. *See, e.g., Jervis B. Webb Co. v. Southern Systems, Inc.*, 742 F.2d 1388, 1392 & n.4, 222 USPQ 943, 945 & n.4 (Fed. Cir. 1984). The only indication that the district court recognized the presumption of validity and its proper application was its statement that "[t]he key issue in this case is whether the defendant has overcome the presumption of nonobviousness." That statement, however, speaks only part of the truth; the presumption of validity goes to validity of the patent in relation to the patent statute *as a whole*, not just to nonobviousness under section 103.

III. *Prior Invention of Another, 35 USC 102(g)*

Section 102(g) states that a person shall be entitled to a patent unless "before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it." Section 102(g) "relates to prior inventorship by another in this country" and "retains the rules governing the determination of priority of invention. . . ." *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1444, 223 USPQ 603, 606 (Fed. Cir. 1984) (quoting P.J. Federico, *Commentary on the New Patent Act*, 35 USCA page 1, at 19 (1954)). Section 102(g) says: "In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other."

Reduction to practice, and conception as well, is a legal determination subject to review free of the clearly erroneous standard. *Barmag Barmer Maschinenfabrik AG v. Murata Machinery, Ltd*, 731 F.2d 831, 837, 221 USPQ, 561, 565-66 (Fed. Cir. 1984); *D.L. Auld Co. v. Chroma Graphics Corp.*, 714 F.2d 1144, 1151, 219 USPQ 13, 18 (Fed. Cir. 1983). Findings of fact supporting that legal conclusion are, of course, reviewed under the clearly erroneous standard.

Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." 1 *Robinson On Patents* 532 (1890); *Coleman v. Dines*, 754 F.2d 353, 359, 224 USPQ 857, 862 (Fed. Cir. 1985). Actual reduction to practice requires that the claimed invention work for its intended purpose, *see, e.g., Great Northern Corp. v. Davis Core & Pad Co.*, 782 F.2d 159, 165, 228 USPQ 356, 358 (Fed. Cir. 1986), and, as has long been the law, constructive reduction to practice occurs when a patent application on the claimed invention is filed. *Weil v. Fritz*, 572 F.2d 856, 865 n.16, 196 USPQ 600, 608 n.16 (CCPA 1978) (citing with approval *Automatic Weighing Machine Co. v. Pneumatic Scale Corp.*, 166 F. 288 (1st Cir. 1909)).

After a review of the record in its entirety, including the numerous corroborating Hybritech laboratory notebooks, internal documents, and pertinent testimony, we hold clearly erroneous the district court's finding that there is no clear or corroborated evidence "with regard to when before May 1980, the idea of actually using monoclonals in sandwich assays" was conceived or, more properly, of when the *claimed invention* was conceived, and therefore reverse the court's holding, as a matter of law, that Hybritech's inventors did not conceive the claimed invention before May 1980.

Hybritech's claim of conception, generally, is evidenced by the sometimes sparsely documented work of a start-up company whose first small advances evolved into the myriad activities of a mature company with efforts directed toward developing the claimed invention by first employing the Kohler and Milstein technology to produce the necessary monoclonal antibodies and using those antibodies in diagnostic sandwich assay kits. There is no doubt that exploiting monoclonal antibodies for use in sandwich assays was one of the major objectives of Hybritech. In a letter to Pharmacia Fine Chemicals dated April 26, 1979, Greene, in responding to Pharmacia's interest in Hybritech's products, outlined the latter's "efforts to bring the exciting new hybridoma technology into routine medical use" and its exploration of "several intriguing concepts for which monoclonals may open up new immunodiagnostic techniques heretofore infeasible with animal serums." Although company minutes in early 1979 contain little about the claimed subject matter and some of the discussions thereon, such as Greene's and Dr. Adams' conversation about monoclonal sandwich assays when the former was trying to woo Dr. Adams to join Hybritech were unrecorded, the Hybritech laboratory notebooks and the nature of Hybritech's research program fully corroborate the testimonial evidence of conception and thus clearly support our holding that Hybritech conceived the claimed invention before LJCRF.

Dr. David's January 1979 notebook describes, in detail, as explained by Greene and Dr. David at trial, a nylon apparatus that undoubtedly could be used for performing a sandwich assay using monoclonal antibodies, although Dr. David testfied on cross-

examination that at that time Hybritech had not yet developed any monoclonal antibodies, including attaching one of the reagents to a solid carrier ring, contacting that ring with a fluid sample in a microtiter plate well, adding a labelled reagent to the well after rinsing, and then "counting" or measuring the amount of either the labelled or unlabelled reagent after a prescribed time and second rinsing. The notebook then describes the procedure for detecting an antibody "(a-x)" to an antigen "(x)" complete with diagrams and text, both illuminated by Dr. David at trial. The notebook further states, "Alternatively, if one wished to quantitate an antigen, y, the identical procedure would be followed, except that reagents would be reversed, i.e. the reaction would be:" and there follows a clear illustration of an antibody attached to a solid carrier reacting with an antigen to form a complex, and that complex reacting with a second labelled antibody. The notebook was signed by Dr. David on January 4, 1979, and witnessed and signed on January 30 of the same year by Dr. Curry, the first cell biologist hired at Hybritech to set up the hybridoma production program.

Dr. David testified on direct that monoclonal antibodies were developed in the following months: antigens were purchased from outside sources and purified before being injected into mice; the spleen cells from those mice were fused with myelomas; and the resultant hybridomas were seperated into well plates for development, and a radioimmunoassay procedure was carried out to determine the affinity of the antibodies.

The May 1979 failed sandwich assay, witnessed in May 1980, corroborates Dr. David's testimony that a polyclonal antibody bound to a solid carrier and a labelled monoclonal antibody were used in a sandwich assay with an antigen from Abbott Labs' Ausria polyclonal diagnostic kit for hepatitis. No binding was detected.

Dr. David testified about the experiment documented in the August 1979 notebook, a sandwich assay with a hepatitis antigen from an Abbott Labs Ausria kit with two Hybritech 068 monoclonal antibodies, one attached to a solid carrier bead and the other labelled; the purpose of the experiment was to quantitate the antigen. The notebook corroborates Dr. David's testi-

mony that the test was positive and lists the counts per minute of the labelled antibody. Defendant Monoclonal's expert Ciotti testified about this experiment:

> Also, of course, it is limited to—it is limited to hepatitis antigen. And without a generic conception, it would just be merely a—if it did work for its intended purpose—which I would assume for purposes of discussion—*it would be a reduction to practice of one embodiment.* And without a corresponding generic conception, I don't think it would be held to be the making of the invention in terms of, for instance, in claim 19. [Emphasis ours.]

Dr. David further testified that the September 21, 1979, record in David's notebook, witnessed months later, shows a reverse sandwich assay using a bound 259 monoclonal antibody and a labelled 068 monoclonal antibody with a hepatitis antigen with results confirmed by a dose response curve.[2] Hybritech further alleges that a laboratory notebook page dated October 1979 is a reduction to practice of the claimed invention but fails to cite any related testimony or other evidence in support thereof.

Finally, the record shows that the claimed affinity limitation "of at least about 10^8 liters/mole" was determined and appreciated during the course of the development of the claimed subject matter. Dr. David and Dr. Adams separately testified that the screening procedures used by Hybritech ensured that only monoclonal antibodies having at least 10^8 liters/mole affinity would be used in assays. An October 1979 internal memorandum from Greene to the staff states, "To improve comparisons we will express all affinities to the base ten to the eighth which represents the lower end of the useable range."

We are left with the definite and firm conviction that a mistake has been committed because the district court's account of the

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[2] A dose response curve is antigen concentration plotted against the signal produced by labelled antibody in an immunoassay. The signal increases with increasing antigen concentration in a successful assay but at some point decreases when the antigen concentration becomes too high.

evidence that "there was no credible evidence of conception before May 1980" is insupportable. There is such evidence. The laboratory notebooks, alone, are enough to show clear error in the findings that underlie the holding that the invention was not conceived before May 1980. That some of the notebooks were not witnessed until a few months to one year after their writing does not make them incredible or necessarily of little corroborative value. Admittedly, Hybritech was a young, growing company in 1979 that failed to have witnesses sign the inventors' notebooks contemporaneously with their writing. Under a reasoned analysis and evaluation of all pertinent evidence, however, we cannot ignore that Hybritech, within a reasonable time thereafter, prudently had researchers other than those who performed the particular experiments witness the notebooks in response to Tom Adams' advice. The notebooks clearly show facts underlying and contemporaneous with conception of the claimed invention and in conjunction with the testimony of Dr. David and Greene, and others, are altogether legally adequate documentary evidence, under the law pertaining to conception, of the formation in the minds of the inventors of a definite and permanent idea of the complete and operative invention as it was thereafter applied in practice. We thus are not moved by Monoclonal's argument that the findings of fact underlying conception are based on credibility determinations and are more sacrosanct than usual. *See Anderson*, supra, at 1512-13.

1. *LJCRF Is Not Prior Art*

Hybritech laboratory notebooks and the uncontradicted testimony of Dr. David and Mr. Greene show that development of the claimed invention proceeded diligently through the rest of 1979 and 1980, there being absolutely no evidence of record nor even argument by Monoclonal that Hybritech was not diligent in its efforts to reduce to practice the claimed invention during the period January 1979 to the '110 application filing date of August 4, 1980. We therefore hold as a matter of law that Hybritech's conception, which was before LJCRF conceived the claimed invention, coupled by diligence to its constructive reduction to practice by the filing of the '110 application, entitle

Hybritech to priority over LJCRF. *See* 35 USC 102(g). The work of LJCRF is therefore not prior art.

We also note that there is inadequate factual basis for the district court's holding that LJCRF reduced the claimed invention to practice as early as November 1979 because the only evidence that corroborates the testimony of Ruoslahti, Uotila, and Engvall is the note from Ruoslahti to Uotila, see section A, 2, supra, which indisputably is not the claimed invention, and the *one* curve from *one* graph from only one page, 43D, of the six Uotila notebooks. After a reasoned examination, analysis, and evaluation of this pertinent evidence we conclude that it falls far short of showing the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice," *see Coleman*, 754 F.2d at 359, 224 USPQ at 862, and therefore is legally inadequate to support even a holding of *conception* of the claimed invention by LJCRF personnel in 1979.

(1) It is undisputed that page 43D was not signed, witnessed, or dated; (2) the deposition testimony of Uotila was that she could not remember the procedure used to arrive at the dose-response curve on page 43D and there was not enough information in her notebook to refresh her memory; (3) the testimony of Ruoslahti was that he could find *no* data in the notebook supporting that graph, none of the *later* graphs shown there represented successful assays and that "especially after this was done, we ran into more severe problems. And it took us a while to do away with the problems;" (4) Ruoslahti also testified that they never determined, in 1979, the affinities of the monoclonal antibodies they used, and that the title of page 43D had been altered at some point—the word "inhibition" had been crossed out and "sandwich" written in; and (5) the testimony of Engvall was that there was nothing about the shape of those curves which indicates that they were sandwich assays. We also note, as evidence bearing upon the credibility of Ruoslahti's testimony (that LJCRF actually reduced the claimed invention to practice in 1979), that when LJCRF attempted to provoke an interference in the PTO with Hybritech based on the U.S. filing of an application that was the counterpart to a Swedish application disclosing similar subject

matter, LJCRF could not demonstrate even a *prima facie* reduction to practice prior to Hybritech's August 4, 1980, filing date. During that proceeding, the earliest dates Ruoslahti set down on paper to support conception and reduction to practice were in 1980.

2. *The Work of Oi/Herzenberg Is Not the Claimed Invention*

It is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention, and that such a determination is one of fact. *See, e.g., Lindemann*, supra, 730 F.2d at 1458, 221 USPQ at 485; *Great Northern Corp. v. Davis Core & Pad Co.*, 782 F.2d 159, 165, 228 USPQ 356, 358 (Fed. Cir. 1986). Section 102(g) upon which the district court relied is one type of "anticipation," i.e., prior invention by another of the same invention. Drs. Oi and Herzenberg testified that their work did not involve detecting the presence of or quantitating antigen but a determination of the number and location of epitopes on a *known* quantity of antigen. Although this work did involve a sandwich assay to the extent that an antigen was sandwiched between two monoclonal antibodies, it is clear that the similarity between that work and the claimed invention goes no further. Furthermore, both doctors testified that they did not know the affinities of the antibodies that were used in their mapping work and in fact never calculated them. Ciotti, Monoclonal's expert, testified that the 10^8 affinity limitation cannot be found anywhere in the Oi/Herzenberg work. Again we are left with a definite and firm conviction that a mistake was made because that work does not meet every element of the claimed invention. The district court's finding to the contrary is clearly erroneous.

We note that the district court, is also holding the patent invalid under § 103, next considered, combined the Oi/Herzenberg work with the Frankel reference, one justifiable inference therefrom being that the court recognized that Frankel discloses a claim *element* that Oi/Herzenberg does not, namely, at least about 10^8 liters/mole affinity.

IV. *Obviousness, 35 USC 103*

A section 103 obviousness determination—whether the claimed invention *would have been* (not "would be" as the court

repeatedly stated because Monoclonal's pretrial papers used that improper language) obvious at the time the invention was made is reviewed free of the clearly erroneous standard although the underlying factual inquiries—scope and content or the prior art, level of ordinary skill in the art,[3] and differences between the prior art and the claimed invention—integral parts of the subjective determination involved in § 103, are reviewed under that standard. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered *before* a conclusion on obviousness is reached and is not merely "icing on the cake," as the district court stated at trial. *See Lindemann*, supra, 730 F.2d at 1461, 221 USPQ at 488; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 219 USPQ 856 (Fed. Cir. 1983); *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 314 (Fed. Cir. 1983).

1. *The Eight Articles "Predicting" Widespread Use of Monoclonal Antibodies*

Before discussing the more pertinent references in this case—the Oi/Herzenberg and Frankel works—we cull the other prior art references relied on by the trial court.

First, the latest four of the eight articles that the court stated were of the "utmost importance" because they "predicted" that the breakthrough in production of monoclonal antibodies by Kohler and Milstein would lead to widespread use of monoclonal antibodies in immunoassays are neither 102(a)/103 nor 102(b)/103 prior art because they are dated between late 1979 and March 6, 1980, well after the date of conception and within one year of the filing date of the '110 patent.

The earliest four of the eight articles, on the other hand, although clearly prior art, discuss *production* of monoclonal

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[3] Although the district court failed expressly to find the level of ordinary skill in the art at the time the invention was made, it did make reference to "[p]eople working in immunology aware of the Kohler and Milstein discovery" which we deem an accurate finding for the purposes of that portion of the *Graham* factual inquiries.

antibodies—admittedly old after Kohler and Milstein showed how to produce them—but none discloses sandwich assays. At *most*, these articles are invitations to try monoclonal antibodies in immunoassays but do not suggest how that end might be accomplished. To the extent the district court relied upon these references to establish that it would have been *obvious to try* monoclonal antibodies of 10^8 liters/mole affinity in a sandwich immunoassay that detects the presence of or quantitates antigen, the court was in error. *See Jones v. Hardy*, 727 F.2d 1524, 1530, 220 USPQ 1021, 1026 (Fed.Cir. 1984) ("Obvious to try" is improper consideration in adjudicating obviousness issue).[4]

2. *The Kohler and Milstein Work, the Cuello Article and the Jeong, Piasio, and Schurr Patents Considered by the Examiner*

The district court's finding that Kohler and Milstein developed a method for producing monoclonal antibodies in vitro is correct, but that finding proves no more; although it made possible all later work in that it paved the way for a supply of monoclonal antibodies, it indisputably does not suggest using monoclonal antibodies in a sandwich assay in accordance with the invention claimed in the '110 patent.

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[4] Finding 10, which states that the invention was contemporaneously developed and disclosed in at least five publications and patent applications not listed above *and dated well after the filing date of the '110 patent but before its issuance* is irrelevant for purposes of the hypothesis based on the three factual inquiries required by § 103 as interpreted by *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966) because obviousness must be determined as of the time the invention was made. Additionally, they are of little probative value in this case because they are dated December 1981 at the earliest, more than a year after the August 4, 1980, filing date here and roughly two years after conception occurred. Furthermore, simultaneous development may or may not be indicative of obviousness, the latter being the case here for the above reasons and because the other evidence of nonobviousness is adequate, such occurrences having been provided for in 35 USC at 135. *Lindemann*, supra, 730 F.2d at 1460-61, 221 USPQ at 487; *Environmental Designs, Ltd. v. Union Oil Co. of California*, 713 F.2d 693, 698 n.7, 218 USPQ 865, 869 n.7 (Fed. Cir. 1983).

The Cuello reference discloses monoclonal antibodies but not in a sandwich assay. The competitive assay in Cuello, moreover, uses only one monoclonal antibody and thus in no way suggests the claimed invention wherein a ternary complex of two monoclonal antibodies and an antigen form a sandwich. Furthermore, the court did not explain how this art, by itself or in combination with any of the other art, suggests the claimed subject matter and thus why that combination would have been obvious. We are of the opinion that it does not.

The district court correctly found that the use of polyclonal antibodies in sandwich assays was well known. The Jeong patent discloses the use of polyclonal antibodies in a simultaneous sandwich assay, with no suggestion that monoclonal antibodies be so used. It is prior art by virtue of § 102(e), application for the patent having been filed September 5, 1978, its effective date as a reference. The Piasio patent, disclosing a reverse sandwich assay using polyclonal antibodies, and Schurrs, disclosing a forward sandwich assay using the same, both § 102(a) prior art, are likewise devoid of any suggestion that monoclonal antibodies can be used in a similar fashion.

3. *The Oi/Herzenberg Work and the Frankel Article*

Clearly, the most pertinent items of prior art not cited by the examiner are the Oi/Herzenberg work, as described in section A, 3, supra, and the Frankel article. As stated in the discussion of Prior Invention of Another (section III, 2, supra), the Oi/Herzenberg work involved mapping epitopes on a known quantity of antigen. It was not concerned with and does not disclose using monoclonal antibodies of at least 10^8 liters/mole affinity. Oi and Herzenberg testified that they did not know the affinity of the antibodies used, and Ciotti testified that nowhere in that work is there mention of monoclonal antibody affinity of at least 10^8 liters/mole. On this basis, we conclude that the Oi/Herzenberg work is qualitatively different than the claimed invention; the former is directed to mapping epitopes on a known quantity of antigen and the latter to determining the "presence or concentration of an antigenic substance in a sample of fluid . . . ." We disagree with Monoclonal that these are "essentially the same thing." Furthermore, it is perfectly clear that this work in no way

suggests using monoclonal antibodies of the affinity claimed in the '110 patent. It is because of these differences between the Oi/Herzenberg work and the claimed invention that the fact that an antigen was sandwiched between two monoclonal antibodies in the course of Oi's and Herzenberg's work is not sufficient basis to conclude that the claimed invention would have been obvious at the time it was made to a person of ordinary skill in the art.

Likewise, a conclusion that the invention would have been obvious cannot properly be reached when the Oi/Herzenberg work is considered in view of the Frankel article. Frankel teaches a method for rapid determination of affinity constants for monoclonal antibodies, some of which clearly have affinities of the order defined by the claims, but does not in any way suggest using two of those antibodies in a sandwich to assay an antigen by forming a ternary complex of labelled antibody, the antigenic substance, and a bound antibody wherein the presence of the antigenic substance is determined by measuring either the amount of labelled antibody bound to a solid carrier or the amount of unreacted labelled antibody. The mere existence of prior art disclosing how to measure the affinity of high affinity monoclonal antibodies is insufficient to support a holding of obviousness. Hybritech's claims define a *process* that *employs* monoclonal antibodies, and does not merely claim antibodies of high affinity. In view of the fact that the Oi/Herzenberg work is not directed to an assay as claimed and does not disclose antibodies of at least 10^8 liters/mole affinity, and further that Frankel fails to suggest using such antibodies in a sandwich assay, the Frankel article does not compensate for the substantial difference between the Oi/Herzenberg work and the claimed subject matter, and therefore those references in combination cannot support a holding of obviousness.

4. *Objective Evidence of Nonobviousness*

In one part of its opinion the court found that "the commercial success of the kits *may* well be attributed to the business expertise and acumen of the plaintiff's personnel, together with its capital base and marketing abilities" (emphasis ours) and later that "[w]here commercial success is based on the sudden availability of starting materials, in this instance the availability of

monoclonal antibodies as a result of the Kohler and Milstein discovery, business acumen, marketing ability, and capital sources, no causal relationship is proven." (Citation omitted.)

i. *Commercial Success: Hybritech's Diagnostic Kits Grabbed a Substantial Market Share*

The undisputed evidence is that Hybritech's diagnostic kits had a substantial market impact. The first diagnostic kit sales occurring in mid-1981, sales increased seven million dollars in just over one year, from $6.9 million in 1983 to an estimated $14.5 million in 1984; sales in 1980 were nonexistent. Competing with products from industry giants such as Abbott Labs, Hoffman LaRoche, Becton-Dickinson, and Baxter-Travenol, Hybritech's HCG kit became the market leader with roughly twenty-five percent of the market at the expense of market shares of the other companies. Its PAP kit ranks second only to a product sold by Dupont's New England Nuclear, surpassing products from Baxter-Travenol, Abbott, and others. Hybritech's other kits, indisputably embodying the invention claimed in the '110 patent, obtained similar substantial market positions.

Although the district court did not provide its insights into why commercial success was due to business acumen and not to the merits of the claimed invention, Monoclonal urges in support that it was due to Hybritech's spending disproportionate sums on marketing, 25-30% of income. The undisputed evidence was that expenditures of *mature* companies in this field are between 17 and 32%. Furthermore, the record shows that advertising makes those in the industry—hospitals, doctors, and clinical laboratories—aware of the diagnostic kits but does not make these potential users buy them; the products have to work, and there is no evidence that that is not the case here or that the success was not due to the merits of the claimed sandwich assays—clearly contrary to the district court's finding.

The trial court's finding that the "sudden availability of monoclonals" was the reason for the commercial success of Hybritech's diagnostic kits (Finding 11) is unsupported by the record and clearly erroneous. Monoclonal admits that monclonal antibodies were available in the United States in *1978*, and the

evidence clearly reflects that. Thus, at least *three years* passed between the time monoclonal antibodies were available in adequate supply and the time Hybritech began selling its kits. Especially in the fast-moving biotechnology field, as the evidence shows, that is anything but sudden availability.

ii. *Unexpected Advantages*

Hybritech points to the testimony of three witnesses skilled in the diagnostic field who state that, based on tests done in their laboratories as a result of real-world comparisons in the normal course of research, the diagnostic kits that embody the '110 invention unexpectedly solved long-standing problems. Dr. Hussa, the head of a large referral laboratory and a world-wide consultant, testified that until Hybritech introduced its kits, he and others were very skeptical and had almost exclusively used competitive assays with a radioactive tracer (RIAs).[5] In relation to an HCG Hybritech kit, he testified that he had first thought that the Hybritech HCG kit would not give accurate results for low antigen concentrations because that condition is indicated in the Hybritech kit by a low radioactivity reading, a reading difficult to differentiate from control samples containing no antigen. He also stated that in the past, RIA kits falsely detected HCG in nonpregnant women, a condition which would indicate cancer and surgery. He stated that when he employed the Hybritech HCG kit in such instances it demonstrated, correctly and absent any difficulty interpreting the data, that no HCG was present.

Dr. Blethen, an M.D. holding a Ph.D. in biochemistry, testified that she did not think that the Hybritech HGH kit, for detecting growth hormone in children, would offer any advantage, but she

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[5] Monoclonal's expert Blakemore testified that of 425 assays on the market in 1979 less than 1% were sandwich assays. Today, sandwich assays constitute the majority of all assays sold.

The record also shows that Blakemore, who testified extensively for Monoclonal that the claimed invention would have been obvious, never used monoclonal antibodies in sandwich assays at Cetus before 1980. Additionally, she did not even mention them in the Jeong patent of which she was a coinventor, which issued January 13, 1981, long after the beginning of Hybritech's work in this area in 1979.

determined that it detected HGH deficiencies in children where conventional RIAs failed to do so. She also stated that the kit does not give false positive readings as do conventional RIA kits, an opinion shared by Dr. Hussa. A third witness, Dr. Herschman, who holds a master's degree in chemistry, testified that he spent years working on the development of an assay that would determine the presence of TSH (thyroid stimulating hormone) with greater sensitivity. He succeeded but discovered that the Hybritech TSH kit had the same sensitivity, the test being performed in four hours rather than the three days his kit required.

Having considered the evidence of nonobviousness required by § 103 and *Graham*, supra, we hold, as a matter of law, that the claimed subject matter of the '110 patent would not have been obvious to one of ordinary skill in the art at the time the invention was made and therefore reverse the court's judgment to the contrary. The large number of references, as a whole, relied upon by the district court to show obviousness, about twenty in number, skirt all around but do not as a whole suggest the claimed invention, which they must, to overcome the presumed validity, *Lindemann*, 730 F.2d at 1462, 221 USPQ at 488, *as a whole*. *See* 35 USC 103; *Jones v. Hardy*, 727 F.2d 1524, 1529, 220 USPQ 1021, 1024 (Fed. Cir. 1984). Focusing on the obviousness of substitutions and differences instead of on the invention as a whole, as the district court did in frequently describing the claimed invention as the mere substitution of monoclonal for polyclonal antibodies in a sandwich assay, was a legally improper way to simplify the difficult determination of obviousness. *See generally Hodosh v. Block Drug Co.* 786 F.2d 1136, 229 USPQ 182 (Fed. Cir. 1986)[6]

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[6] It bears repeating that it is crucial that counsel set forth the law accurately. More particularly, it is the duty of counsel to impart to the judge that the obviousness question properly is whether the *claimed* invention *as a whole would have been* obvious to one of *ordinary* skill in the art *at the time the invention was made*, and that the district court must *expressly* make the three factual determinations required by *Graham* and consider objective evidence of obviousness *before* the legal conclusion of obviousness vel non is made. Submitting to the court

With respect to the objective indicia of nonobviousness, while there is evidence that marketing and financing played a role in the success of Hybritech's kits, as they do with any product, it is clear to us on the entire record that the commercial success here was due to the merits of the claimed invention. It cannot be argued on this record that Hybritech's success would have been as great and as prolonged as admittedly it has been if that success were not due to the merits of the invention. The evidence is that these kits compete successfully with numerous others for the trust of persons who have to make fast, accurate, and safe diagnoses. This is not the kind of merchandise that can be sold by advertising hyperbole.

V. *Enablement, Best Mode, and Definiteness Under § 112*

The section 112 defense appears to have been an afterthought of both Monoclonal, who briefly but unsuccessfully attempts to defend this utterly baseless determination, and of the district court which adopted the defense from Monoclonal's pretrial papers apparently without knowledge of the applicable law, to highlight, as it stated at trial, that it was part of its job to see that "whoever wins wins all the way or whoever loses loses all the way." Taken as a whole, the court's comments on § 112—split into two parts, one from Monoclonal's pretrial brief and the other from the adopted pretrial findings and conclusions—are internally inconsistent. The opinion states that the patent fails to disclose how (1) to make monoclonal antibodies; (2) to screen for proper monoclonal antibodies; and (3) to measure monoclonal antibody affinity and therefore the specification is nonenabling and does not satisfy the best mode requirement, and the claims are indefinite. We discuss each of these in turn.

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language like "any differences . . . would have been obvious," as was done here, violates the axiom that the question is not whether the differences would have been obvious but the claimed invention *as a whole*. Furthermore, arguing that "it would be obvious" rather than that it would *have been* obvious shifts the court's focus to the wrong period of time, namely to a time long after the invention was made, in which, more likely than not, the prior art and the level of ordinary skill in the art are more advanced. *See* 35 USC 103.

1. *Enablement*

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention, *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 960, 220 USPQ 592, 599 (Fed. Cir. 1983), is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive, *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984), and is determined as of the filing date of the patent application, which was August 4, 1980. *See W. L. Gore and Associates v. Garlock, Inc.*, 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983). Furthermore, a patent need not teach, and preferably omits, what is well known in the art. *Lindemann*, 730 F.2d at 1463, 221 USPQ at 489.

The record fully supports the '110 patent's statement that

> The monoclonal antibodies used for the present invention are obtained by the [hybridoma] process discussed by Milstein and Kohler . . . . The details of this process are well known and not repeated here.

The district court itself stated that the "method for producing monoclonal antibodies in vitro was well known prior to the alleged invention of the '110 patent," and used the "sudden availability of monoclonal antibodies" produced by the Kohler and Milstein discovery to support, albeit erroneously, its finding of a lack of nexus between the merits of the claimed invention and its commercial success. The court then about-faced and held the '110 patent deficient because it fails to teach how to make monoclonal antibodies.

With respect to screening, the only permissible view of the evidence is that screening methods used to identify the necessary characteristics, including affinity, of the monoclonal antibodies used in the invention were known in the art and that the '110 patent contemplated one of those. At trial, Monoclonal's counsel stated "it is a procedure that was known in '78." In similar fashion, the district court held that the claimed subject matter would have been obvious in part because the "existence of monoclonal antibodies *having the affinity constants claimed in the*

patent was well known prior to the alleged invention . . . ." [Emphasis ours.] Furthermore, there was not a shred of evidence that undue experimentation was required by those skilled in the art to practice the invention. We hold as a matter of law that the '110 patent disclosure is enabling.

2. *Best Mode*

"The specification . . . shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 USC 112. Because not complying with the best mode requirement amounts to concealing the preferred mode contemplated by the applicant at the time of filing, in order to find that the best mode requirement is not satisfied, it must be shown that the applicant knew of and concealed a better mode than he disclosed. *DeGeorge v. Bernier,* 768 F.2d 1318, 1324, 226 USPQ 758, 763 (Fed. Cir. 1985) (quoting with approval *In re Sherwood,* 613 F.2d 769, 135 USPQ 311 (CCPA 1962)). The only evidence even colorably relating to concealment is testimony by various Hybritech employees that sophisticated, competent people perform the screening and that the screening process is labor-intensive and time-consuming. It is not plausible that this evidence amounts to proof of concealment of a best mode for screening or producing monoclonal antibodies for use in the claimed '110 process, and therefore we are of the firm conviction that the district court's finding that the best mode requirement was not satisfied is clearly erroneous.

3. *Indefiniteness*

The basis of the district court's holding that the claims are indefinite is that "they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency." (Conclusion 6.) Even if the district court's finding in support of this holding—that "there is no standard set of experimental conditions which are used to estimate affinities"—is accurate, under the law pertaining to indefiniteness—"if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more," *Shatterproof Glass Corp. v. Libbey*

Owens Ford Co., 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir. 1985)—the claims clearly are definite. The evidence of record indisputably shows that calculating affinity was known in the art at the time of filing, and notwithstanding the fact that those calculations are not precise, or "standard," the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more.

VI. *Motions*

Monoclonal's motion to strike Appendices A and B of Hybritech's reply brief as being beyond the page limit applicable to reply briefs is granted as to Appendix A but denied as to Appendix B, the latter having been helpful in culling the often non-supportive citations to the record by Monoclonal.

Hybritech's motion to supplement the record with a Monoclonal advertisement not considered at trial is denied. Any adverse impact that the disposition of these two motions has upon either party is more than outweighed by this court's patience with the seemingly endless flow of post-argument argumentative papers.

VII. *Conclusion*

The judgment of the district court holding the patent in suit invalid is *reversed* in all respects, and the case is *remanded* for a determination of the issue of infringement which the court held was moot.

REVERSED AND REMANDED

Appendix B

Hybritech Incorporated, a
California corporation, Plaintiff,
v.
Monoclonal Antibodies, Inc., a
California corporation, Defendant.

No. C-84-0930 SC.

United States District Court,
N.D. California.

Aug. 28, 1985.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

CONTI, District Judge.

This case came on regularly for trial on the 5th day of August, 1985, without a jury, and the trial consumed fifteen days. Plaintiff was represented by Lyon & Lyon of Los Angeles, California, and defendant was represented by Cartwright, Sucherman, & Slobodin, and Flehr, Hohbach, Test, Albritton & Herbert, of San Francisco, California.

The following exposition and later contents herein are all to be considered the court's Findings of Fact and Conclusions of Law.

The Parties

This is a suit by plaintiff Hybritech, Inc. for alleged infringement by defendant Monoclonal Anitibodies, Inc. of U.S. Patent No. 4,376,110, entitled "Immunometric Assays Using Monoclonal Antibodies," issued March 8, 1983, to Gary S. David and Howard E. Greene, on application filed August 4, 1980 (hereinafter referred to as the "'110" patent). The plaintiff, Hybritech, commenced its operations in 1979, and the defendant, Monoclonal Antibodies, Inc. (hereinafter sometimes referred to as MAB) also commenced its operations in 1979; both companies are involved in the development, production and sale of diagnostic kits. While the plaintiff markets a broad range of these kits, defendant's kits are limited for pregnancy and ovulation.

The Patent in Suit

The patent in suit is directed to an alleged invention by Dr. Gary David, an immunochemist, and Ted Greene, a science graduate who has worked in management, relating to the development of diagnostic products.

The patent in suit concerns the use of monoclonal antibodies in sandwich assays. Monoclonal antibodies are genetically engineered cells called "hybridomas". These hybridoma cells are produced by fusing mouse spleen cells and malignant mouse cells (called Myelomas). The said patent, cells and assays will be more fully discussed hereinafter.

The invention is a process for determining the presence of, or the amount of, antigen in a fluid sample, such as a patient's blood or urine. An antigen is a substance, usually a protein or carbohydrate, that when introduced into the body stimulates the production of an antibody. One example of an antigen is a foreign substance in the body which causes disease, such as a virus. Another is a substance which evidences a condition of the body. For example, the antigen IgE (immunoglobulin E) is an indication of an allergy condition; the antigen CEA (Carcinoembryonic Antigen) is an indication of colon cancer; and the antigen hCG (human Chorionic Gonadotropin) is an indication of pregnancy. Generally, an antibody may be defined as a substance produced by the body's immune system in response to the presence of a foreign antigen.

The invention of the patent, sometimes called a "sandwich" or "two-site" assay, is a method of analyzing fluids for antigens, employing certain antibodies called "monoclonal antibodies", and taking advantage of their unique properties to obtain an extremely fast, sensitive and accurate analysis. The key issue in this case is whether the defendant has overcome the presumption of non-obviousness.

The subject matter of this patent deals principally with the medical field of immunology, i.e., the workings of the body's immune system.

One of the miraculous processes of the body is its immune system. Each cell in the body has a distinct shape on its surface that distinguishes it from foreign cells. The body's army, its immune system, controls unfamiliar shapes using special troops made in the bone marrow. Certain blood or plasma cells known as lymphocytes learn to recognize the foreign molecular structure of the foreign cell or substance known as the antigen and produce antibodies which lock on to the antigen. The antigen or harmful foreign substance which "raises" the antibody is then rendered harmless in various ways. The antibody/antigen reaction is still not well understood by scientists but it may be thought of as a lock and key fitting arrangement. An antibody at its reactive site is a shape which fits and locks onto a corresponding site on the antigen known as an epitope.

The body has millions of different kinds of lymphocytes each capable of producing an antibody of a very particular structure for the purpose of seeking out a single epitope on an antigen. Once the body is invaded by an antigen a lymphocyte which produces an antibody specific for that antigen will reproduce or clone itself in vast numbers so that a large supply of antibodies to conquer the invader may be produced. These antibodies will be specific for a particular epitope on the antigen. These antibodies being of identical molecular structure, all being made of the same clones, may be termed monoclonal antibodies. However, in the body of an animal, even though monoclonal antibodies are produced by the animal, they are always found together with other antibodies. Therefore, when the blood or serum of an animal is taken for its antibodies, the mixture found is known as "polyclonal antibodies" because it is derived from different (poly)-clones.

Introduction of an antigen into the body is termed "immunization" because it stimulates production of polyclonal antibodies which can cause immunity to the infection caused by that antigen. Most antigens are also complex and have a large number of distinct epitopes. One characteristic of an antibody is its specificity or ability to bind to a particular epitope. Another characteristic is sensitivity, defined as the smallest amount of antigen that can be detected by the antibody. Sensitivity is related to a theoretical characteristic known as affinity, which is a

measure of the binding strength of an antibody for its antigen. While affinity calculations can be made for simple or small molecules, it is very difficult to do for large, complex molecules involving extremely complex reactions and can only be estimated. Also, the affinity estimations vary to a significant extent, depending upon the conditions of experiments used for the estimations.

Although the polyclonal antibodies were and are effective tools for use in immunoassay, they had certain disadvantages. If the animal died, the source of antibodies was gone and no one knew how antibodies from a different animal would compare. Also, the immune system of the animal could suddenly change the type of antibody being produced. Thus, supply of antibodies was limited and uncertain.

Since it was known that the body produced "monoclonal antibodies" within the body or "in vivo", scientists knew that if they could produce these monoclonal antibodies outside of the body or "in vitro", these problems and others would be solved. However, the plasma cells making the antibodies would not live outside of the animal and the concept of large scale production of monoclonal antibodies was only a dream until Kohler and Milstein produced their classic paper in 1975 based on a discovery they had made on how to produce monoclonal antibodies. For this work, Kohler and Milstein in 1984 received a Nobel prize.

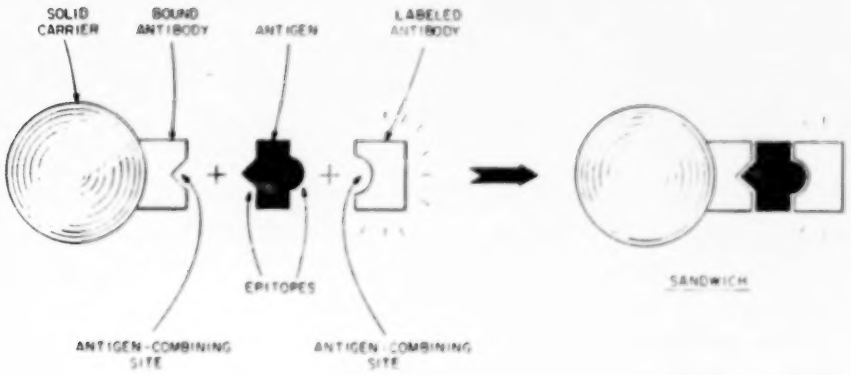
Georges Kohler and Cesar Milstein took a tumor consisting of cancer cells which grew in vitro and fused them with normal antibody producing cells. The fusion resulted in what is called a hybridoma cell. These hybridoma cells could survive, and be cultured in vitro. Through the use of other techniques, the individual hybridoma cells could be segregated and the segregated individual cells could be cloned. These clones produce antibody molecules of identical structure or monoclonal antibodies. Suddenly, it became possible to produce tailor-made, highly specific monoclonal antibodies in vast quantities. The obvious uses for diagnostic purposes of these monoclonal antibodies became evident to those in the scientific and commercial world.

Two well-known diagnostic assay procedures using polyclonal antibodies in the prior art included "competitive assays" and

"sandwich assays". In a competitive assay for an antigen in a sample, a known quantity of the same antigen is labelled. In a competitive assay for an antigen, the limited amount of antibody is bound to a solid surface. The sample containing an unknown amount of antigen is contacted with the antibody together with a known amount of labelled antigen. The labelled antigen will "compete" with any unlabelled antigen to react with the bound antibody. If there is no antigen in the test sample, all of the antigen attached to the antibody will be labelled. The greater the amount of antigen in the test sample, the less the amount of labelled antigen there will be detected. Since only a limited amount of antibody is required, this competitive test was popular with polyclonal antibodies because of the difficulty of obtaining large amount of antibodies.

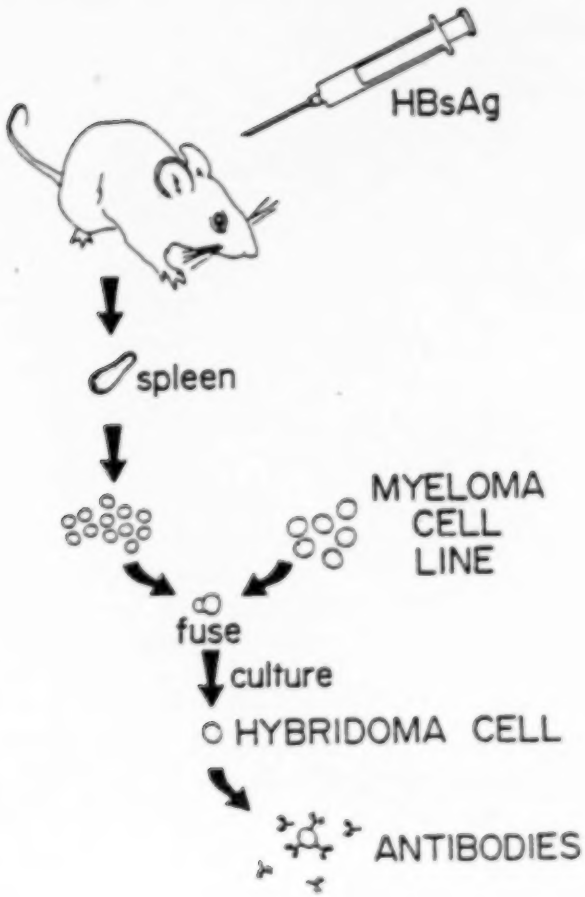
In one form of the sandwich assay for the antigen, a large amount of antibody is bound to the solid surface and it is exposed to the test sample containing the unknown amount of antigen. If antigen with epitopes recognized by the antibody is present, it should bind to the antibody on the solid surface. At that point, labelled antibody, also in excess amount, is added to the solution. The labelled antibody will now bind to an epitope on another part of the antigen, thus the formation of a sandwich. See Figure 1. If all of the reagents, i.e., reacting materials, antibodies and antigen, are added at the same time, it would be termed a simultaneous sandwich assay. All of this was known to the prior art.

FIGURE 1—SANDWICH ASSAY



People working in immunology aware of the Kohler and Milstein discovery, knew that monoclonal antibodies could be used in place of polyconal antibodies in virtually every use to which the polyclonals had been put, e.g., monoclonal antibodies in a sandwich assay. While the idea was a simple one, putting it into practice was time consuming, and expensive, because of the steps necessary to produce the monoclonals for commercial diagnostic purposes. There are a number of complex steps to be gone through before such kit would be available. Suitable screening assays must be developed to select the best antibody-producing clones from perhaps hundreds of thousands of them. The sheer work and time involved in "cell forming" is also considerable.

The following is a schematic illustration of hybridoma formation. Monoclonal antibody is produced against hepatitis B surface antigen (HBs-Ag).



It was not too long before various entrepreneurs in this country decided that this technology would be worth exploiting. While the concept, e.g., of using monoclonal antibodies in a sandwich assay was simple and obvious, the work and technology involved in coming up with the right antibody, testing for it, finding economically feasible ways to attach antibody to solid surface to label antibody, would be difficult and expensive.

A Stanford MBA, named Thomas Glaze, decided in the summer of 1978 that he would form a company (the defendant company herein) to produce monoclonal antibodies to replace polyclonal antibodies in diagnostics. Mr. Glaze, as evidenced by his business plan, intended to contact certain customers who were using sandwich assays with polyclonal antibodies. The defendant Monoclonal Antibodies, Inc. (MAB) was formed in April, 1979. The evidence indicated discussions in the fall of 1979 involving the use of monoclonal antibodies in sandwich assays. In March of 1980, MAB began selling monoclonals and informed others, both orally and in writing, that sandwich assays were included among their potential uses. Plaintiff's patent application was not filed until August 4, 1980, and the patent did not issue until March 8, 1983. Without any knowledge of the activities at Hybritech, MAB on its own, developed commercial kits using monoclonal antibodies in sandwich assays. After obtaining government approval, MAB, in November of 1982, had a kit on the market.

An experienced marketing manager with an MBA from Harvard, named Ted Greene, had similar ideas. He was brought in in early 1979 to become president and chief executive officer of Hybritech, Inc. (Hybritech), a company which had been formed a few months earlier, also to develop monoclonal antibodies to be used in place of polyclonals. While the Hybritech people had considered the various uses to which the new monoclonal antibody tool could be put, one of which was in assays such as a sandwich assay, they had not yet decided exactly what they would be doing regarding monoclonal antibodies in diagnostics. They did, however, know that they were going to develop monoclonal antibodies antigens and they began to do so. At no time before May of 1980, is there any documentation whatsoever which even suggests that the idea at Hybritech of using monoclonal antibo-

dies in sandwich assays would be innovative. Nor is there any clear or corroborated testimony with regard to when before May of 1980, the idea of actually using monoclonals in sandwich assays was first discussed.

During the time frame in question, at least five different groups of workers in the field employed sandwich assays using monoclonal antibodies. For example, at La Jolla Cancer Research Foundation (LJCRF) a team of scientists headed by Dr. Ruoslahti and including Drs. Engvall and Dr. Uotila, developed and ran a simultaneous sandwich assay using monoclonal antibodies. Laboratory notebooks proved this was done no later than November 5, 1979. This work was submitted to two respected scientific journals and published in November of 1980 in the Journal of Immunological Methods. At the exact same time that this work was going on, Hybritech, then a fairly small company, had its offices and shared space and equipment with LJCRF.

As early as July 1978, and merely because monoclonal antibodies were available at the Stanford University Laboratory of Dr. Herzenberg, a sandwich assay using monoclonal antibodies was performed. This work was published in December 1979, in a Journal called Molecular Immunology. The sandwich assay was one of a series of diagnostic procedures set forth by Dr. Herzenberg, who did not single out the sandwich assay as anything out of the ordinary.

Hybritech, by the spring of 1980, had raised many millions of dollars with the backing of venture capitalists. They were thus able to afford and hire a man of vast experience in diagnostics and patents by the name of Dr. Thomas Adams. This was done in April 1979.

One of the first things Adams wanted to know as an executive of Hybritech was what subject matter there was that the company could patent. In a memorandum to Greene on April 25, 1980, re "patentable ideas", Adams, after setting forth a few ideas stated:

> Also can we try for a general patent on the use of labelled monoclonal Ab [antibody] or coating with monoclonals if we can show meaningful advantages over conventional antiserum?

As of April 25, 1980, even though they discussed patentable ideas, there is no mention of the subject matter of the patent in suit. Dr. Adams then decreed that every technical worker at Hybritech should have an idea notebook. On April 28, Dr. Gary David, Hybritech's chief scientist, wrote a number of entries in his "idea notebook", none of which included the subject matter in question. May 6 is his first entry which suggests only that the simultaneous assay using monoclonal antibodies is new. In the same month, experiments were carried out, so that now Hybritech had reached the point where they, too, had run a simultaneous sandwich assay using monoclonal antibodies.

In the first review of the patent application by the U.S. Patent and Trademark Office (PTO), the Patent Examiner rejected all of the originally filed claims as being obvious under Section 103 of the patent statute (35 U.S.C. § 103) in view of the Cuello prior art reference, alone or in combination with other prior art references. The Cuello reference disclosed using monoclonal antibodies in an immunoassay and the other references disclosed sandwich assays using polyclonal antibodies. The Examiner pointed out that Hybritech's application conceded that the sandwich assay protocols of the claim are old and concluded "... it would be obvious to use the monoclonal antibody for the polyclonal antibodies in the conventional immunoassay protocols defined by the instant claims ..."

As hereinabove noted, competitive and sandwich assays are similar. In Cuello, monoclonal antibodies were used in a competitive type assay.

Hybritech's attorney argued that based upon the differences between a competitive and a sandwich assay, it would not be obvious to use the monoclonal antibodies of Cuello in the sandwich assay. The Examiner was not convinced by the arguments, and again (the second time) rejected the claims on grounds similar to the first rejection.

Hybritech's attorney then amended the broadest claims to include a numerical limitation (at least 10^8 liters/mole) regarding the affinity (strength of binding) of the antibodies to corresponding antigen and restated his arguments. Hybritech's

attorney supported his argument with a declaration from Richard Bartholomew, a Hybritech employee, alleging certain advantages of using monoclonal antibodies rather than polyclonal antibodies in sandwich assays.

It is obvious that in order to perform in a sandwich assay, the antibodies have to be of high affinity. Hybritech used 10^8 liters/mole as the arbitrary cutoff point in their selection of antibodies for further testing during the antibody development phase. It was well known that high affinity antibodies were required for these assays in the prior art.

The so-called reasons for allowance were not well-founded because (1) the alleged advantages were expected as naturally flowing from the well-known natural characteristics of monoclonal antibodies compared to polyclonal antibodies; (2) alleged advantages were not significant but argued to the Examiner as if they were; or (3) were at best minor advantages of certain monoclonal antibody sandwich assays and not applicable to all monoclonal antibodies as claimed by Hybritech.

The credible testimony of J. Blakemore indicated that the reasons for the final granting of the patent by the Examiner were not scientifically valid and misplaced.

It is of the utmost importance to be aware that shortly after Kohler and Milstein's discovery made monoclonal antibodies known and they became available, their advantageous use in various immunoassays was predicted by a number of authorities, none cited by the Patent Office.

A 1978 edition of Cellular Immunology, in a chapter relating to monoclonal antibodies, Drs. Herzenberg and Milstein, is stated at page 25.1: "Apparently inexhaustible supplies of pure, specific, standardized antibody can now be assured for almost any clinical or laboratory immunoassay."

In January 1979, in Chemical and Engineering News, is stated: "... [A]dapting monoclonal antibodies to radioimmunoassay [immunoassays using radioactive labels] that are widely used in clinical tests is a predictable, potentially important development ..."

In early March, 1980, in Nature, in an article dealing with immunometric or sandwich assays, Dr. Ekins stated: ". . . Combined in the exploitation of the in vitro hybridoma techniques of antibody production pioneered by . . [Kohler and Milstein] . . . with which large quantities of monospecific antibodies can be produced, the emergence of simple and reliable assay procedures far surpassed current . . [competitive assays] . . in sensitivity, precision, speed, specificity and overall reliability is within sight . . . "

In his February 1980 article in Clinical Microbiology Newsletter, Dr. Sevier of Hybritech, stated under the hearing "Uses in Immunoassay: "An essentially unlimited supply of monoclonal antibodies, precisely defined according to amount and affinity, will lead to major improvements and innovations in immunochemical techniques. For immunodiagnostics, monoclonal antibodies will improve performance, reduce costs and open up types of immunological testing. More obvious advances will include: . . . Antibodies for use with . . . enzyme . . . immunoassays . . ."

Furthermore, as conceded by Hybritech, the sandwich assay procedures using polyclonal antibodies were well known in the orders of addition of antibody to antigen of the patent in suit. (See, e.g., the simultaneous assay of the Jeong patent 4,244,940).

In addition, monoclonal antibodies of affinity in excess of 10^9 liters/mole were known (Frankel and Gerhard article in Molecular Immunology, DX:AB), as was the desirability of polyclonal antibodies of such affinity in immunoassays, including sandwich assays.

In December, 1979, Oi and Herzenberg published an article in Molecular Immunology disclosing the use of monoclonal antibodies in a sandwich assay based upon work performed in 1978 and submitted for publication in April 1979. The article refers to the subject matter of the patent in suit merely as a modification of a radioimmunoassay, i.e., other well-known technology.

Authority Regarding Validity

A. *Obviousness:*

Section 103 provides as follows:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. . . .

The Patent Examiner felt the subject matter was obvious and only changed his mind in reliance on the Bartholomew Declaration. He did not have available the various references noted before. The trial testimony of experts indicate the bases for the issuance of the patent by the Examiner was incorrect. (See testimony of J. Blakemore).

In view of the foregoing, it would be obvious to substitute in a known sandwich assay, known high affinity monoclonal antibodies for polyclonal antibodies of similar affinity for the known advantages of monoclonal antibodies over polyclonal antibodies in immunoassays.

B. *Prior Invention of Others*

Plaintiff's patent is invalid under 35 U.S.C. § 102(g):

> ". . . before the applicant's invention thereof the invention was made in this country by another who has not abandoned, suppressed, or concealeed it."

Based on the above facts, the simultaneous sandwich assay using high affinity monoclonal antibodies (greater than 10^9 liters/mole) was reduced to practice by LJCRF in the United States as early as November, 1979, long prior to the August 4, 1980 filing date of the '110 patent. LJCRF continued the work on the project by conducting further experiments, and preparing papers and patent applications which ultimately were filed and published. Even if such reduction to practice were secret, it would invalidate the patent if the inventon was not abandoned, suppressed or concealed. LJCRF did not abandon, suppress or

conceal since steps were taken to make the invention publicly known and it diligently pursued publication and filed a patent application. Therefore, the Foundation's reduction to practice constitutes prior art under 35 U.S.C. § 102(g) and is prior art at least as early as November 5, 1979.

The same is also true for the work of Oi and Herzenberg, where the reduction to practice took place in July of 1978.

Hybritech did not establish an earlier date of invention than the above two mentioned references since there is no credible evidence of conception prior to May of 1980.

C. *Invalidity under 35 U.S.C. § 112*

The limitation of an affinity for the antigen of at least about 10^8 liters/mole is present in all of the '110 patent claims, and was added by amendment during prosecution in response to the first rejection by the Examiner. Also, the affinity limitation was cited by the Examiner as a reason for allowance. In spite of this significance attributed to it during prosecution, the specification fails to teach how to obtain monoclonal antibodies having such affinities or why the limitation is significant. The first paragraph of Section 112 requires a written description of the invention in sufficient detail so that one can perform it. The specification fails to disclose how to measure affinities (if they can be "measured" rather than merely estimated). Also, it fails to disclose whether affinity is determined (1) when the antibodies are in their natural form as produced by the hybridoma, or (2) after the antibodies are either bound to the support surface or attached to the labelled antibody.

The first paragraph of Section 112 also requires applicant to set forth the best mode contemplated by the inventor for carrying out his invention. However, the specification fails to disclose how to form and screen the many hybridoma cells lines to identify those hybridoma that produce antibodies having the specified affinities.

Under the second paragraph of Section 112, the claims must particularly point out and distinctly claim the invention. As discussed above, the specification of the '110 patent does not disclose any method for determining the affinities of monoclonal

antibodies. The definiteness requirement of § 112 is not met if the patent does not disclose to the public how infringement may be avoided. *Norton Company v. Bendix Corporation,* 449 F.2d 553, 555 (2d Cir.1971). Since the antibody affinity was inserted as a limitation in all of the broadest (independent) claims of the '110 patent and argued by Hybritech to be a critical limitation, those of ordinary skill in the art must be able to determine this number with certainty in order to determine whether they are infringing. There is no standard set of experimental conditions which are used to estimate affinities and the variations in the values which are estimated.

The court, in reaching its conclusion that the patent in issue is invalid, is persuaded by the credible testimony of Dr. Vernon Oi, Judy Blakemore, Thomas Ciotti, Dr. Scott Monroe, Dr. Leonard Hertzenberg, Dr. Ruoslahti, and Dr. Amshey.

Laughton Miles in the late 1960's made known the sandwich assay with the use of monoclonal antibodies.

Kohler and Milstein gave the know-how for the development of monoclonal antibodies.

All the modes of assay were known by the prior art. The testing kits and procedure prior to Kohler and Milstein used polyclonal antibodies, and once Kohler and Milstein invented the technology for developing monoclonal antibodies, it was obvious to use monoclonal antibodies in a sandwich assay where polyclonal antibodies had been used in the past.

The testimony of plaintiff's own witness and co-inventor of the patent in suit, in discussing the key elements of the patent, stated: the patent states that you need antibodies with high affinity—yet he says this was known in the prior art. Also, he (David) says you need remote sites on the antigen; however, a sandwich assay to work well must have remote sites—this is obvious, and yet the patent does not tell you how t do this—David went on to state that this was known in the literature. In sum, you screen till you get two antibodies that work in an assay.

Even the witness for plaintiff, Dr. Nisonoff, stated that "once monoclonal antibodies were known it would be logical and ex-

pected that moncolonal antibodies would reach equilibrium faster because of the known physical properties of monoclonal antibodies, and if you were working with monoclonal antibodies you would consider their affinity when thinking of diagnostic uses.

Dr. L. Hertzenberg, Ph.D, and with a world-wide reputation, and who worked in the Milstein laboratory in England, stated that in 1977 he did a sandwich assay with monoclonal antibodies. Hertzenberg stated that the monoclonal assay was obvious.

It is the court's conclusion that the major advance was the invention of Kohler and Milstein in the making of monoclonal antibodies, that is the ability to clone a cell to the properties you want and to have that clone cell live forever.

Once the scientific community had the monoclonal antibody it was obvious and logical to those expert in the field to use them in known assays as substitutes for products (polyclonal antibodies) of inferior qualities.

The plaintiff has not sustained the burden of proof with the requisite corroborative evidence as to the "date of conception" or the date of "Reduction to Practice".

The court further finds that plaintiff's contention to rebut obviousness, to wit: the commercial success of the kits re the patent in suit, is unpersuasive. Commercial success, to be meaningful indicia of unobviousness, must be related directly to the claimed inventions. Here the court finds that the commercial success of the kits may well be attributed to the business expertise and acumen of the plaintiff's personnel, together with its capital base and marketing abilities. Business success is not the ultimate criteria for unobviousness.

The defendant has not been able to sustain its burden of proof re inequitable conduct on the part of the defendant.

The matter of infringement is moot, as the court finds the patent in issue invalid.

The court makes further findings of fact and conclusions of law, even though some of the following findings and conclusions are

repetitive to the foregoing, for the sake of completeness and to give due reference to the facts that the court has found.

1. Plaintiff, Hybritech, Inc. (hereinafter "Hybritech") is a corporation organized and existing under the laws of the State of California and has its place of business at 11085 Torreyana Road, San Diego, California.

2. Defendant, Monoclonal Antibodies, Inc. (hereinafter "Monoclonal"), is a corporation organized and existing under the laws of the State of California and has its principal place of business at 2319 Charleston Road, Mountain View, California.

3. This is an action for infringement of U.S. Letters Patent No. 4,376,110 (hereinafter the "'110 patent").

4. The application for the '110 patent was filed August 4, 1980, and named Gary S. David and Howard E. Green as joint inventors. It issued March 8, 1983 and was assigned to Hybritech. It relates to the use of monoclonal antibodies having affinities of at least 10^8 liters/mole in sandwich assays for detecting antigens. The antigen is sandwiched between a bound antibody on a solid carrier and a labelled antibody. Claims 1-9 are directed to a reverse sandwich assay in which the labelled antibody is reacted with the antigen prior to contact with the bound antibody. Claims 10-18 are directed to a simultaneous sandwich assay in which the antibodies and antigen are reacted simultaneously. Claim 19 is directed to the sandwich assay without specifying the order of addition of reagents. Claims 20-29 are dependent on claim 20.

5. As conceded by Hybritech in the patent, the use of polyclonal antibodies in sandwich assays was well known prior to the alleged invention of the '110 patent with various orders of addition of reagents, including the reverse and simultaneous mode. U.S. Patent No. 4,244,940 (Defendant's Exhibit A) to Jeong, it al., issued January 13, 1981, discloses a simultaneous sandwich assay using polyclonal antibodies. U.S. Patent No. 4,098,876 to Piasio, et al., issued July 4, 1978, discloses a reverse sandwich assay using polyclonal antibodies. U.S. Patent No. 4,016,143 to Shuurs, et al., issued April 5, 1977, discloses a forward sandwich assay using polyclonal antibodies.

6. A method for producing monoclonal antibodies in vitro was well known prior to the alleged invention of the '110 patent. This method was disclosed first in an August 7, 1975 publication in Nature, Vol. 256, pp. 495-497, by G. Kohler and C. Milstein entitled "Continuous Cultures of Fused Cells Secreting Antibody of Predetermined Specificity." (Testimony of Blakemore, Defendant's Exhibit AL.)

7. The existence of monoclonal antibodies having the affinity constants claimed in the '110 patent was well known prior to the alleged invention of the '110 patent. For example, monoclonal antibodies having affinities of greater than 10^8 and some greater than 10^9 liters/mole were disclosed in a February 1979 publication in Molecular Immunonology, Vol. 16, pp. 101-106 by M.E. Frankel and W. Gerhard entitled "The Rapid Determination of Binding Constance for Anti-Viral Antibodies by a Radioimmunoassay." Defendant's Exhibit AB—per Blakemore testimony.

8. The use of monoclonal antibodies in competitive assays ("RIA"), was well known prior to the alleged invention of the '110 patent. This use was disclosed in a July 1979 publication in the proceedings of the National Academy of Science, Vol. 76, No. 7, pp. 3532-3536, by A.C. Cuello, G. Galfre and C. Milstein, entitled "Detection of Substance P in the Central Nervous System by a Monoclonal Antibody". Defendant's Exhibit V.

9. Sandwich assays using monoclonal antibodies were disclosed in a December 1979 publication in Molecular Immuniology Vol. 16, pp. 1005-1017, by V.T. Oi and L.A. Herzenberg, entitled "Localization of Murine Ig-Ib and Ib-Ia (IgG_{2a})Allotypic Determinants Detected with Monoclonal Antibodies", long prior to the alleged invention of the '110 patent.

10. The alleged invention of the '110 patent was contemporaneously developed by at least five different groups of workers in the field and was disclosed in various patent applications and publications between the filing date and the issue date of the '110 patent. For example, European Pat.App. No. 81220768 (defendant's Exhibit G), Akvo N.V. published February 3, 1982, Bulletin 82/5; European Pat.App. No. 81302809.0 (defendant's Exhibit H), Unilever N.V., published December 30, 1981, Bulle-

tin 82/52; European Pat.App. No. 81106832.9, La Jolla Cancer Research Foundation, published March 31, 1982, Bulletin 82/13; and P.C.T.App.P.C.T./US 81/01270, (defendant's Exhibit N) Massachusetts General Hospital, published April 1, 1982, all disclose sandwich assays using monoclonal antibodies.

11. Shortly after the Kohler and Milstein disclosure of monoclonal antibodies stated in Finding 6, the use of monoclonal antibodies in immunoassays was expected and predicted by numerous authorities and commentators in the field. For example, the following publications predicted the use of monoclonal antibodies in immunoassays:

(a) The 1978 publication in Handbook of Experimental Immunology, D. Weir, Editor, Blackwell Scientific Publications, Oxford, pp. 25.1-25.7, by L.A. Herzenberg and C. Milstein entitled "Cell Hybrids of Myelomas with Antibody Forming Cells and T-Lymphocytes with T-Cells", states: "The recent adaptation of cell hybridization techniques to the construction of myeloma-like cell lines producing monoclonal antibodies with desired reactivities has essentially revolutionized the approach to production and utilization of immunospecific reagents. Apparently inexhaustible supplies of pure, specific, standardized antibody can now be assured for almost any clinical or laboratory immunoassay."

(b) The January 1979 publication in Chemical and Engineering News, Vol. 57, No. 1, by J.L. Fox entitled "Antibody Reagents Revolutionizing Immunology" states ". . . [A]dapting monoclonal antibodies to radioimmunoassays that are widely used in clinical tests is a predictable, important development . . ." (Defendant's Exhibit AA).

(c) The June 1979 publication in AJEBAK, Vol. 57, Part 3, pp. 231-344 by G.F. Mitchell et al., entitled "Hybridoma Antibody Immunoassays for the Detection of Parasitic Infection: Development of a Model System Using a Larval Cestode Infection in Mice" states: "Monoclonal antibodies derived from anti-parasite antibody-secreting hybridoma cell lines will be of particular use in the development of new, highly specific, immu-

nodiagnostic reagents for the detection of parasite infection, exposure and disease." (Defendant's Exhibit A).

(d) The 1979 publication in Antibodies in Human Diagnosis and Therapy, E. Haber and R.M. Krause, editors, Raven Press, New York, pp. 225-236 by N.R. Klinman, G.P. Segal, W. Gerhard, T. Braciale and R. Levy, entitled "Obtaining Homogeneous Antibody of Desired Specificity from Fragment Cultures" states: "Perhaps the most obvious of antibodies of a known restricted specificity would be diagnostic." (Defendant's Exhibit AE).

(e) The winter 1979 publication in Ligand Review, Vol. 1, No. 2, by D.S. Skelly entitled "Antibodies: New Developments", states: "The use of monospecific antibodies in immunodiagnostic testing is obvious." (Defendant's Exhibit BE).

(f) The February 1980 publication in The Yale Journal of Medicine, Vol. 53, pp. 71-83 by A. Baumgarten entitled "Viral Immunodiagnosis" states ". . . The specificity and uniformity of monoclonal antibodies should markedly improve diagnostic accuracy . . ."

(g) The February 1980 publication in Clinical Microbiology Newsletter, Vol. 2, No. 3, pp. 1-2 by D.E. Sevier, an employee of plaintiff, entitled "Revolutionary Reagents: Monoclonal Antibodies from Hybridomas" states: "An essentially unlimited supply of monoclonal antibodies, precisely defined according to amount and affinity, will lead to major improvements and innovations in immuno medicine techniques. For immunodiagnostics monoclonal antibodies will improve performance, reduce costs and open up types of immunological testing. More obvious advances will include: . . . antibodies for use with . . . enzyme . . . immunoassays . . ." (Defendant's Exhibit BB).

(h) The March 6, 1980 publication in Nature, Vol. 284, p. 14 by R. Ekins, entitled "More Sensitive Immunoassays", states "Combined with the exploitation of the in vitro hybridoma techniques of antibody production pioneered by Milstein and his colleagues at Cambridge . . . with which large quantities of monospecific antibodies can be produced, the emergence of simple and reliable assay procedures far surpassing current RIA

techniques in sensitivity, precision, speed, specificity, convenience and overall reliability is within sight."

12. The prior art stated in Findings 7, 9 and 11 was not considered during prosecution of the application. This art was more pertinent than the art considered by the Examiner.

13. Any commercial success of the patent was caused by the sudden availability of a new reagent, monoclonal antibodies, together with further reasons hereinabove stated.

14. The primary advantages of monoclonal-based sandwich assays are due to the inherent, known and expected properties of monoclonal antibodies. Any other advantages, expected or not, are insignificant in comparison to the primary advantages.

15. Any differences between the prior art stated in Findings 5, 6, and 7, viewed with or without the prior art stated in Finding 11, and the '110 patent, would have been obvious to one of ordinary skill in the immunoassay art at the time the alleged invention of the '110 patent was made.

16. Any differences between the prior art stated in Findings 7 and 9, viewed with or without the prior art stated in Finding 11, and the '110 patent, would have been obvious to one skilled in the immunoassay art at the time the alleged invention was made.

17. Any differences between the prior art stated in Findings 5, 6, 7 and 8, viewed with or without the prior art stated in Finding 11, and the '110 patent, would have been obvious to one skilled in the immunoassay art at the time the alleged invention was made.

18. A simultaneous sandwich assay using monoclonal antibodies having affinity constants greater than 10^9 liters/mole was reduced to practice by researchers M. Uotilla and E. Ruoslahti at La Jolla Cancer Research Foundation in the United States as early as November 1979.

19. The reduction to practice of Finding 18 resulted in the preparation and publication of an article in The Journal of Immunological Methods in 1981 by them, and the preparation and the filing of a patent application in Sweden in 1980 by Pharmacia, which was assigned to the Foundation.

20. A sandwich assay using monoclonal antibodies was reduced to practice by Vernon Oi at Stanford University in July 1978.

21. This reduction to practice of Finding 20 resulted in a publication in the Journal of Immunology in 1978 and a publication in Molecular Immunology in December 1979.

22. The reductions to practice set forth in Findings 18 and 20 were not abandoned, suppressed or concealed.

23. The claims of the '110 patent are not limited in scope to particular antibodies or concentrations.

24. The specification of the '110 patent fails to disclose how to measure affinities and fails to disclose whether affinity is determined (1) when the antibodies are in their natural form as produced by the hybridoma or (2) after the antibodies are either bound to the support surface or attached to the label.

25. The specification of the '110 patent fails to disclose how to form and screen the many hybridoma cell lines resulting from cell fusion and to identify the particular hybridoma-producing antibodies having the affinities required to practice the processes claimed.

CONCLUSIONS OF LAW

1. The '110 patent is invalid under 35 U.S.C. § 103 in view of the December 1979 publication by V.T. Oi and L.A. Herzenberg, and the February 1979 publication by M.E. Frankel and W. Gerhard. *Lear Siegler, Inc. v. Aeroquip Corp. et al.*, 733 F.2d 881 (Fed.Cir.1984); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452 (Fed.Cir.1984). With respect to the secondary considerations relevant to a determination of obviousness, where the primary advantages of the invention are known and expected, unexpected other advantages cannot rebut evidence of obviousness. *In re Nolan*, 553 F.2d 1261 (CCPA 1977). Finally, commercial success must be related to the claimed invention. Where commercial success is based on the sudden availability of starting materials, in this instance the availability of monoclonal antibodies as a result of the Kohler and

Milstein discovery, business acumen, marketing ability, and capital sources, no causal relationship is proven. *Technograph Printed Circuits Ltd. v. United States,* 164 USPQ 584 (Comm'r Op.Ct.Cl.1970).

2. The said patent is invalid because it teaches nothing new in the art, the art alleged to be taught was obvious and logical to anyone skilled in the field.

3. The '110 patent is invalid under 35 U.S.C. §§ 102(g), 103, in view of prior "inventions" and teachings.

4. The '110 patent is invalid under 35 U.S.C. § 112, first paragraph, because it fails to disclose the best mode known to Hybritech of screening hybridomas to obtain appropriate monoclonal antibodies, and fails to disclose the best mode known to the applicant of forming the hybridomas to be used in the production of monoclonal antibodies.

5. The '110 patent is invalid under 35 U.S.C. § 112, first paragraph, because it fails to teach how to measure affinity and fails to disclose whether affinity is determined when the antibodies are in their natural form or after being bound to a support or attached to a label.

6. The '110 patent is invalid under 35 U.S.C. § 113, second paragraph, because the claims are indefinite; they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency. *Norton Co. v. Bendix Corp.,* 449 F.2d 553 (2d Cir. 1971).

7. The defendant has proven patent invalidity and prior invention by clear and convincing evidence.

8. Defendant's kits do not infringe the '110 patent because of the said patent's invalidity.

Judgment is granted in favor of defendant and against plaintiff. Defendant shall be entitled to its costs.

Appendix C

United States Court of Appeals for the Federal Circuit

Appeal No. 86-531

Hybritech, Incorporated,
Appellant,

v.

Monoclonal Antibodies, Inc.
Appellee.

Judgment

On Appeal from the United States District Court for the Northern District of California

in Case No(s).

C-84-0930-SC

This Cause having been heard and considered, it is Ordered and Adjudged:

REVERSED AND REMANDED

Dated Sep. 19, 1986

entered by order of the Court
/s/ FRANCIS X. GINDHART
Francis X. Gindhart, Clerk

Issued as a Mandate: November 24, 1986

Appendix D

United States Court of Appeals for the Federal Circuit

Appeal No. 86-531

Hybritech Incorporated,

Appellant,

v.

Monoclonal Antibodies, Inc.,

Appellee.

Before Rich, Davis, and Smith, Circuit Judges.

ORDER

A petition for rehearing having been filed in this case, upon consideration thereof, it is

Ordered that the petition for rehearing be, and the same hereby is, denied.

FOR THE COURT

/s/ FRANCIS X. GINDHART
Francis X. Gindhart, Clerk

11/7/86
Date

cc: Mr. Douglas E. Olson
Mr. David J. Brezner

Appendix E

United States District Court
Northern District of California

No. C-84-0930 SC

Hybritech, Inc.,
a California Corporation,
Plaintiff,

vs.

Monoclonal Antibodies, Inc.,
a California Corporation,
Defendant.

Order of Recusal

[Filed Dec. 17, 1986]

Pursuant to Local Rule F(2), the undersigned Judge hereby recuses himself in the above entitled action, and requests that said action be reassigned to another Judge of this Court.

Dated: December 16, 1986.

/s/ Samuel Conti
United States District Judge

Appendix F

APPLICABLE CONSTITUTIONAL PROVISIONS, STATUTES, AND RULES

U.S. Constitution, Article I, Section 8, Clause 8

The Congress shall have power . . . To promote the progress of science and useful arts, by securing for limited times to authors and inventors, the exclusive right to their respective writings and discoveries.

U.S. Constitution, Amendment V

"No person shall . . . be deprived of life, liberty or property, without due process of law. . . ."

35 U.S.C., Section 102(g)

Conditions for patentability; novelty and loss of right to patent.

A person shall be entitled to a patent unless—

> (g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of the one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

35 U.S.C., Section 103

Conditions for patentability; non-obvious subject matter.

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

. . . .

Federal Rules of Civil Procedure, Rule 52(a)—Findings by the Court

(a) *Effect.* In all actions tried upon the facts without a jury or with an advisory jury, the court shall find the facts specially and state separately its conclusions of law thereon, and judgment shall be entered pursuant to Rule 58; and in granting or refusing interlocutory injunctions the court shall similarly set forth the findings of fact and conclusions of law which constitute the grounds of its action. Requests for findings are not necessary for purposes of review. Findings of fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge the credibility of the witnesses. . . .

APPENDIX G

United States Patent [19] [11] 4,376,110
David et al. [45] Mar. 8, 1983

[54] IMMUNOMETRIC ASSAYS USING MONOCLONAL ANTIBODIES

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[73] Assignee: Hybritech, Incorporated, La Jolla Calif.

[21] Appl. No.: 175,133
[22] Filed: Aug. 4 1980
[51] Int. Cl.³ G01N 33/54; G01N 33/56
[52] U.S. Cl. 436/513; 435/7; 436/548; 436/529; 436/540
[58] Field of Search ..... 23/230 B; 424/12, 1, 424/8, 435/7

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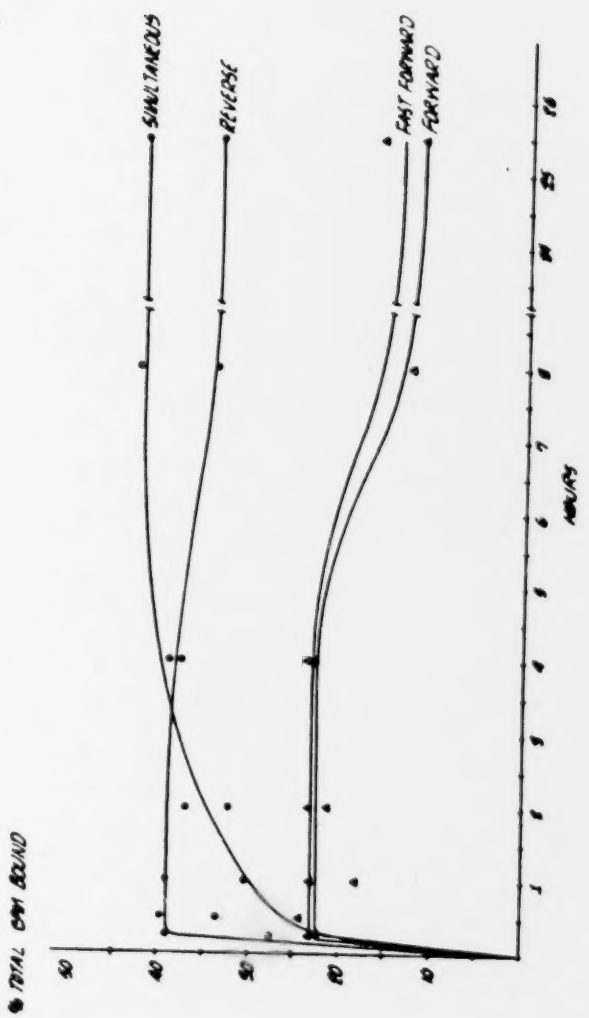
A.C. Cuello et al., Proc. Natl. Acad. Sci. U.S.A., vol. 76(7), 3532-3536 (Jul. 1979).

Primary Examiner—Sidney Marantz
Attorney, Agent, or Firm—Lyon & Lyon

[57] ABSTRACT

"Two-site" or "sandwich" immunometric assay techniques for determination of the presence and/or concentration of antigenic substances in fluids using monoclonal antibodies. One monoclonal antibody is presented in a soluble labeled form and a second monoclonal antibody is presented bound to a solid carrier; the soluble and bound monoclonal antibodies may be the products of either the same or different cell lines. Each monoclonal antibody has an affinity for the antigenic substances of at least about 10^8 liters/mole.

29 Claims, 2 Drawing Figures



U.S. Patent Mar. 8, 1983 Sheet 1 of 2 4,376,110

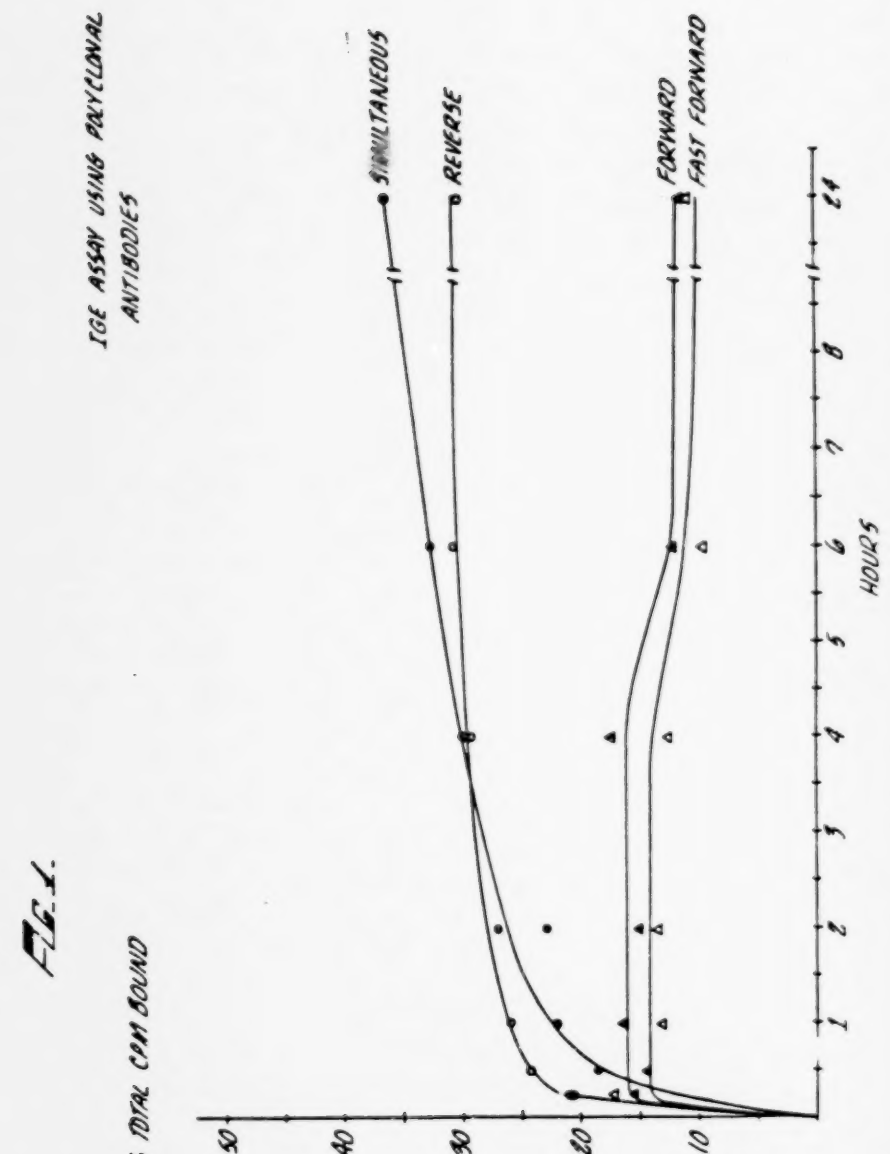


FIG. 1.

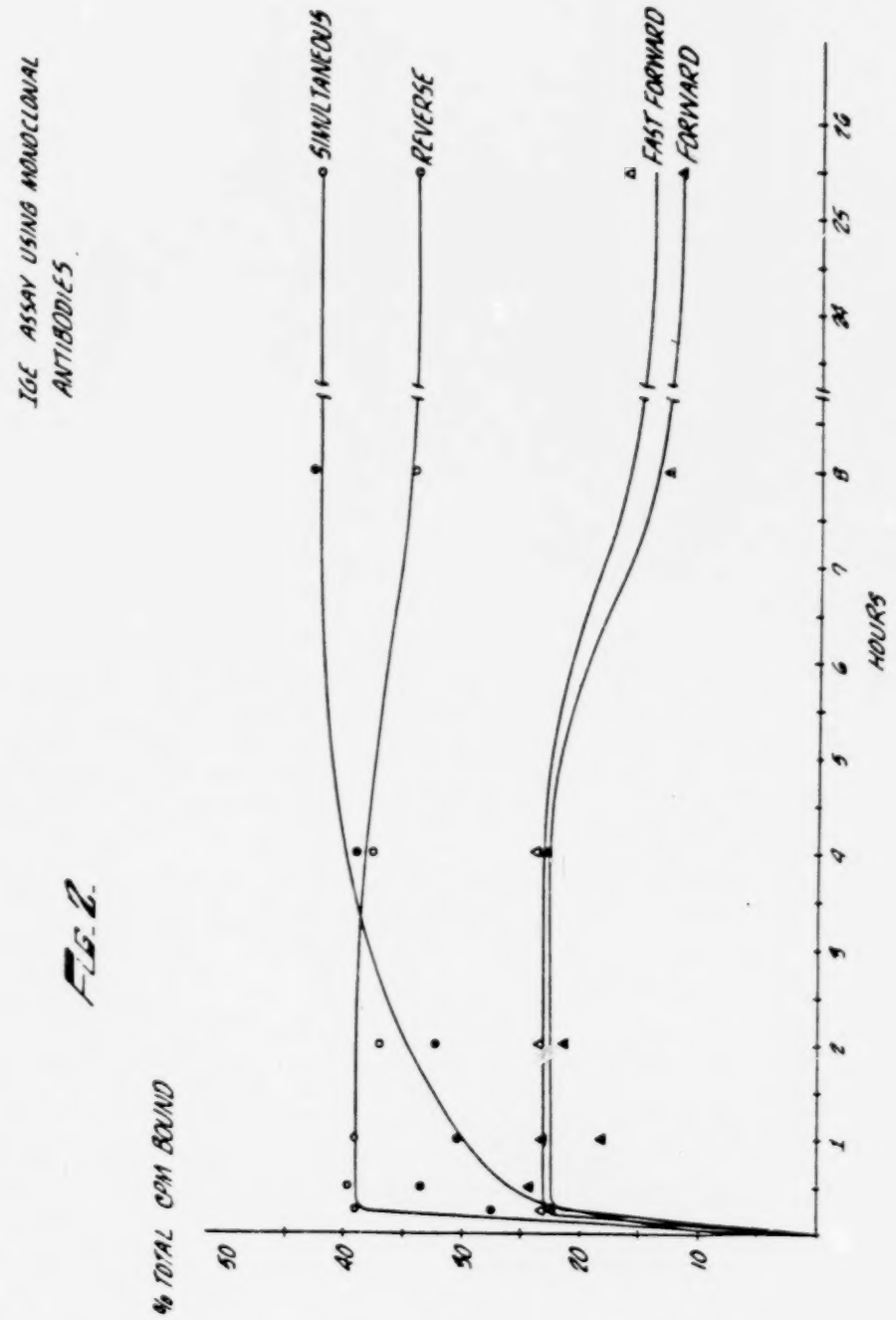

IGE ASSAY USING MONOCLONAL ANTIBODIES
SIMULTANEOUS
REVERSE
FAST FORWARD
FORWARD
% TOTAL CPM BOUND
HOURS
50
40
30
20
10
1
2
3
4
5
6
7
8
11
24
25
16

FIG. 2.

IMMUNOMETRIC ASSAYS USING MONOCLONAL ANTIBODIES

FIELD OF THE INVENTION

This invention relates to methods for detecting and/or determining the concentration of antigenic substances in fluids such as serum. In another aspect it relates to immunometric assay techniques. In yet another aspect it relates to monoclonal antibodies.

BACKGROUND

The determination of the presence or concentration of antigenic substances, for example, those associated with a wide variety of physiological disorders, in serum or other body fluids relies increasingly upon immunoassay techniques. These techniques are based upon formation of a complex between the antigenic substance being assayed and an antibody or antibodies in which one or the other member of the complex may be labelled, for example, by a radioactive element such as I^{125}, which permits its detection and/or quantitative analysis after separation of the complexed labelled antigen or antibody from uncomplexed labelled antigen or antibody.

In the case of a competition immunoassay technique, the antigenic substance in a sample of fluid being tested for its presence competes with a known quantity of labelled antigen for a limited quantity of antibody binding sites. Thus, the amount of labelled antigen bound to the antibody is inversely proportional to the amount of antigen in the sample. By contrast, immunometric assays employ a labelled antibody. In such an assay, the amount of labelled antibody associated with the complex is directly proportional to the amount of antigenic substance in the fluid sample.

Immunometric assays have been found to be particularly well suited for the detection of polyvalent antigens, i.e., antigenic substances that are able to complex with two or more antibodies at the same time. Such assays employ a quantity of unlabelled antibody bound to a solid support that is insoluble in the fluid being tested and a quantity of soluble antibody bearing a label

such as a radioactive isotope that permits detection and/or a quantitative estimate of the amount of the ternary complex formed between solid phase antibody, antigen, and labelled antibody.

In immunometric assays known to the prior art, typically a "forward" assay, in which the antibody bound to the solid phase is first contacted with the sample being tested to extract the antigen from the sample by formation of a binary solid phase antibody: antigen complex, is employed. After a suitable incubation period, the solid support is washed to remove the residue of the fluid sample, including unreacted antigen if any, and then contacted with a solution containing a known quantity of labelled antibody.

After a second incubation period to permit the labelled antibody to complex with the antigen bound to the solid support through the unlabelled antibody, the solid support is washed a second time to remove the unreacted labelled antibody. In a simple "yes/no" assay to determine whether the antigen is present in the sample being tested, the washed solid support is tested to detect the presence of labelled antibody, for example, by measuring emitted radiation if the label is a radioactive element. The amount of labelled antibody detected is compared to that for a negative control sample known to be free of the antigen. Detection of labelled antibody in amounts substantially above the background levels indicated by the negative control is interpreted to indicate the presence of the suspect antigen. Quantitative determinations can be made by comparing the measure of labelled antibody with that obtained for standard samples containing known quantities of the antigen.

This kind of assay is frequently referred to as a "two-site" or "sandwich" assay since the antigen has two antibodies bonded to its surface at different locations. This and related techniques are described by Wide at pp. 199-206 of "Radioimmunoassay Methods", Edited by Kirkham and Hunter, E. & S. Livingstone, Edinburgh, 1970. An assay based on this technique for the detection of the antigen associated with serum hepatitis using an 125_I labelled antibody is described in U.S. Pat. No. 3,867,517.

Despite their great utility, the prior art immunometric assays have been recognized to be slow procedures, in part because two washing steps are required and because lengthy incubation periods are required to reach equilibrium, i.e., the point at which the amount of complex formed does not change with increasing time.

To eliminate at least one of the washing steps associated with this procedure, so-called "simultaneous" and "reverse" assays have been proposed. A simultaneous assay involves a single incubation step as the antibody bound to the solid support and the labelled antibody are both added to the sample being tested at the same time. After the incubation is completed, the solid support is washed to remove the residue of fluid sample and uncomplexed labelled antibody. The presence of labelled antibody associated with the solid support is then determined as it would be in a conventional "forward" sandwich assay.

A reverse assay involves the stepwise addition first of a solution of labelled antibody to the fluid sample followed by the addition of unlabelled antibody bound to a solid support after a suitable incubation period. After a second incubation, the solid phase is washed in conventional fashion to free it of the residue of the sample being tested and the solution of unreacted labelled antibody. The determination of labelled antibody associated with the solid support is then determined as in the simultaneous and forward assays.

Both the simultaneous and reverse assay techniques require a sufficient excess amount of solid phase antibody to bind most or all of the antigen present to avoid a high dose hook effect where artificially negative or low quantitation of antigen is observed at extremely high concentrations of antigen. For this reason, the forward assay has been the approach preferred by the prior art. That is because large amounts of highly purified, active antibody specific to the antigen of interest for preparing a solid phase with sufficient antigen binding capacity is difficult to obtain from the "polyclonal" antibodies used in prior art processes. Methods for affinity purifying such antibodies have generally been time consuming and resulted in low yields and loss of high affinity antibodies. When an immunogenic substance is introduced into a living body, the body's immune system reacts by generating

antibodies to every site on the immunogen it recognizes. A large immunogenic protein molecule may have dozens of sites and a foreign cell may have hundreds. Thus, while each antibody producing cell produces antibody specific for a single antigenic site the immune system has generated a specie of specific antibody producing cells for each immunogenic site recognized. In addition, the body has produced relatively large quantities of antibodies to antigens other than the one of interest such that most of the antibody in the polyclonal mixture is not specific for the antigen of interest. Accordingly, the antibodies used in prior immunometric assays are necessarily "polyclonal" in nature since the antibodies are derived from antisera raised in a conventional manner in animals and their purification is difficult.

When employing conventional polyclonal antibody mixtures in the reverse and simultaneous assays, the formation of a "sandwich" comprising the antigen complexed by two or more labelled antibodies which complex with the antigen at different sites is possible. These complexes could remain soluble in the sample being tested, be removed by subsequent washing steps, and not "counted" when the solid phase is analyzed for solid phase bound labelled antibody. If this happens to a significant extent, sensitivity of the assay is reduced and erroneous results may arise. However, if the unlabelled bound antibody is added to the sample first as in the forward sandwich assay, steric considerations prevent formation of a sandwich comprising the antigen complexed to two or more unlabelled antibodies where labelled antibody is excluded from also binding to the antigen. Accordingly, the antigen is free to react with a labelled antibody molecule. Nevertheless, it has been proposed to use a simultaneous assay for human thyroid stimulating hormone (HTSH) by employing a large excess of the unlabelled antibody bound to a solid phase to minimize formation by soluble labelled antibodies. See Jeong et al., "Comparison to Radioimmunoassay (RIA) with a Unique, Single-incubation Two-Site Immunoradiometric Assay (IRMA) as Applied to the Determination of Human Thyroid Stimulating Hormone (HTSH)", Bio-Rad Laboratories, 1979.

It has also been proposed to use a reverse assay for HTSH, hepatitis associated antigen (HAA) and carcinoembryonic anti-

gen (CEA) by employing a quantity of labelled antibody sufficient to assure a labelled antibody:antigen complex but insufficient to form a "sandwich" of all the antigen present in a sample. See U.S. Pat. No. 4,098,876.

Since all three of the procedures known to the prior art use a polyclonal mixture of antibodies, the potential for cross-reaction with other materials in serum or other fluid than the antigen for which the test is intended is increased. The occurrence of cross-reactivity with other antigens also reduces the sensitivity of the test for the suspect antigen and increases the prospect of a "false-positive" assay. Furthermore, the use of polyclonal antibodies in a simultaneous or reverse assay requires a careful consideration of the amount of labelled antibody used relative to the amount of solid phase antibody and/or antigen present.

In view of these shortcomings, the limitations to the immunometric procedures known to the prior art are readily apparent. The conventional forward assay is time consuming; the simultaneous and reverse assays are accomplished with fewer steps but require large quantities of solid-phase specific antibody and are not well suited to determination of small concentrations of antigen since formation of a sandwich of the antigen with a multiple number of labelled antibody molecules competes with formation of the sandwich comprising bound antibody:antigen:labelled antibody; and all are subject to misinterpretation of false-positives due to the polyclonal nature of the antibody.

Accordingly, one object of the present invention is to provide an improved process for the immunometric assay for antigenic substances.

More specifically, an object of the present invention is to provide more rapid immunometric assay techniques.

Another object of the present invention is to provide more sensitive immunometric assay techniques.

Yet another object of the present invention is to provide improved "simultaneous" and "reverse" immunometric assays.

The manner in which these and other objects are realized by the present invention will be apparent from the summary and detailed description set forth below.

SUMMARY OF THE INVENTION

According to the present invention, the polyclonal antibody used in an immunometric assay as the unlabelled antibody bound to a solid support and the antibody used as the soluble labelled antibody are replaced by at least one and usually two or more different monoclonal antibodies, i.e., each antibody specific to a single antigenic site and separately produced by clones derived from unique cell lines. In a preferred embodiment of the invention, the monoclonal antibody used as the antibody bound to the solid support is the product of a different cell line than is the monoclonal antibody used for the labelled antibody and the two monoclonal antibodies are selected to bind the antigenic substance at sites remote from each other so as to not interfere with the others binding to the antigen. The advantages of the present invention, particularly in simultaneous and reverse assays, over prior art methods will become clear after consideration of the accompanying drawings and the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph illustrating the results obtained using polyclonal antibodies in four types of immunometric assay for human IgE.

FIG. 2 is a similar graph illustrating the difference in results obtained using monoclonal antibodies in the same four types of immunometric assay for human IgE.

DETAILED DESCRIPTION OF THE INVENTION

As indicated above, according to the present invention, the polyclonal antibody used in an immunometric assay for an antigenic substance is replaced by a monoclonal antibody. The present invention is useful for the determination of the presence

or concentration of a wide variety of polyvalent antigenic substances. Accordingly, as used herein, the term antigen or antigenic substance refers broadly to substances to which antibodies can be produced. Among such substances may be mentioned haptens, hormones such as insulin and human thyroid stimulating hormone (HTSH), gamma globulins, allergens, viruses, virus subunits, bacteria, toxins such as those associated with tetanus and with animal venoms, and even some drugs. Among the specific antigens which may be assayed by the process of the present invention may be mentioned carcinoembryonic antigen (CEA), hepatitis A and B, hepatitis Non A/Non B, IgE and alphafetoprotein.

The monoclonal antibodies useful in the present invention are obtained by the process discussed by Milstein and Kohler and reported in Nature 256 495-497, 1975. The details of this process are well known and will not be repeated here. However, basically it involves injecting a mouse, or other suitable animal, with an immunogen. The mouse is subsequently sacrificed and cells taken from its spleen are fused with myeloma cells. The result is a hybrid cell, referred to as a "hybridoma", that reproduces in vitro. The population of hybridomas are screened to isolate individual clones each of which secrete a single antibody species to the antigen. The individual antibody species obtained in this way are each the product of a single B cell from the immune animal generated in response to a specific antigenic site recognized on the immunogenic substance.

When an immunogenic substance is introduced into a living host, the host's immune system responds by producing antibodies to all the recognizable sites on the substance. This "shotgun" approach to producing antibodies to combat the invader results in the production of antibodies of differing affinities and specificities for the immunogenic substance. Accordingly, after the different hybridoma cell lines are screened to identify those that produce antibody to the desired antigen, the antibodies produced by the individual hybridoma cell lines are preferably screened to identify those having the highest affinity for the immunogenic substance stimulating their original production before selection for use in the present invention. Selection based on this criterion is believed

to help provide the increased sensitivity in the immunometric assay of the present invention using monoclonal antibody compared to the polyclonal antibody used in the prior art which, at best, has an affinity for the antigen which is roughly the average of the affinities of all antibodies produced by the immune system. Preferably, the monoclonal antibody selected will have an affinity of at least 10^8 liters/mole and, more preferably, an affinity of at least about 10^9 liters/mole.

Furthermore, those monoclonal antibodies having the highest affinities can be further screened by running a simulated assay on specimens known to give false positive results with processes employing conventional polyclonal antibodies to identify those monoclonal antibodies which do not cross-react and give false positive results.

Because the two-site immunometric assay relies upon formation of an antibody:antigen:antibody sandwich, usually two different monoclonal antibodies which do not interfere with the binding of each other to the antigen are selected to be the bound antibody and the soluble labelled antibody. Since both are necessary to complete the sandwich, reverse and simultaneous assays can be conducted without concern that a complex of labelled antibody:antigen:labelled antibody will form which will preclude formation of a complex between the antigen and the antibody bound to the solid phase and therein lies a particular advantage of the present invention. Furthermore, a forward assay can be accomplished without the intermediate washing step since the two antibodies bind to different sites. We refer to such a process as a "fast forward" assay.

However, particularly in the case of a forward assay, the same monoclonal antibody can be used for both the labelled antibody and the antibody bound to the solid support when the antigenic substance possesses identical antibody binding sites sufficiently remote from each other to allow more than one antibody molecule to be bound at the same time. In such a system the addition first of the bound antibody to the sample precludes formation of a sandwich because of steric considerations. When the labelled monoclonal antibody is subsequently added, it is also able to

complex with the antigen bound to unlabelled antibody on the solid phase.

The unlabelled monoclonal antibody used in the presence of the present invention to extract the antigenic substance from the sample being tested may be immobilized on any of the common supports used in immunometric assays. Among these may be mentioned filter paper, plastic beads or test tubes made from polyethylene, polystyrene, polypropylene or other suitable material. Also useful are particulate materials such as agarose, cross-linked dextran, and other polysaccharides. The techniques for such bonding are well known to those skilled in the art. For example, antibodies may be bound to polysaccharide polymers using the process described in U.S. Pat. No. 3,645,852.

The labelled monoclonal antibody used in the present invention may be provided with the same labels used in prior art immunometric assays. Among these may be mentioned fluorogenic labels for detection by fluorimetry as described in U.S. Pat. No. 3,940,475 and enzymatic markers as described in U.S. Pat. No. 3,645,090. It is presently preferred to label the antibody with a radioisotope such as I^{125} using, for example, the procedure of Hunter and Greenwood, *Nature*, 144 (1962), page 945 or that of David et al., Biochemistry, Vol. 13, pp. 1014-1021, 1974.

In a typical assay, the amount of labelled antibody associated with the insoluable sandwich complex is determined by examination of the insoluble carrier material by suitable means. However, it is also possible to relate the presence or absence of antigen in the fluid sample being assayed to the amount of labelled antibody which does not react during the assay and remains in a soluble form.

The advantages of the present invention in which monoclonal antibodies are used in immunometric assays as compared to polyclonal antibodies are seen by reference to the following example. In this example, four comparative assays, a simultaneous assay, a reverse assay, a forward assay, and a "fast" forward assay, were run using both monoclonal antibody and polyclonal antibody using a standard serum containing 100 IU/ml of human

IgE as the positive sample. Normal horse serum containing no IgE was used as a negative control.

The polyclonal antibody to IgE used, as the labelled antibody in the example was obtained from Pharmacia Diagnostics of Piscataway, New Jersey. The polyclonal antibody bound to the solid support was obtained from Tago, Inc. of Burlingame, California.

Monclonal antibody to IgE was obtained using the method of Milstein and Kohler discussed above. The two antibodies selected each exhibited an affinity for IgE of greater than 10^9 liter/mole and did not interfere with the others binding to IgE.

The assays were run using unlabelled antibody bound to agarose by the process of U.S. Pat. No. 3,645,852. Labelling of antibody was by 125_I according to the process of David et al., referred to above. Phosphate buffered saline, pH 7.4, was used to wash all samples.

EXAMPLE

(1) Simultaneous Assay Method

Duplicate samples were run in which 100 µl of a suspension of antibody immobilized on agarose particles is mixed with 100 µl of specimen (serum) and 100 µl of soluble ^{125}I-labelled antibody. This mixture as incubated for the specified times shown in Table I (for polyclonal antibody) and Table II (for monoclonal antibody) set forth below, plus 30 minutes. The extra 30 minutes incubation period was added to equalize this assay method with the other assay methods which required an additional 30 minute incubation time for a second added reagent. Following the incubation periods the agarose particles were washed by addition of buffer and centrifuged. After removal of the washing liquid by aspiration, the resulting pellet of agarose particles was then counted for bound ^{125}I-labelled antibody. The counts obtained for each of the complexes after the specified incubation time are set forth in Tables I and II.

(2) Reverse Assay Method

Duplicate samples were run in which 100 µl of specimen (serum) is mixed with 100 µl of ^{125}I-labelled soluble antibody and

incubated for the specified times shown in Tables I and II. 100 µl of a suspension of antibody immobilized on agarose particles is then added and the mixture was allowed to incubate for another 30 minutes. The agarose particles were then washed and counted as in the simultaneous assay method. The counts are reported in Tables I and II.

(3) Forward Assay Method

Duplicate samples were run in which 100 µl of specimen (serum) is mixed with 100 µl of a suspension of antibody immobilized on agarose particles and incubated for the specified times shown in Tables I and II. The agarose particles were then washed once by the addition of 2.5-3.0 ml of buffer which, after mixing, was centrifuged, and the liquid removed by aspiration. 100 µl of ^{125}I-labelled soluble antibody was then added and the mixture incubated an additional 30 minutes. The agarose particles were then washed and counted as in the simultaneous assay method. The counts were reported in Tables I and II.

(4) Fast Forward Assay Method

The assay was performed, in duplicate, in a similar manner to the forward assay method except that the wash step between the initial incubation of specimen with antibody immobilized on agarose particles and the addition of soluble ^{125}I-labelled antibody was omitted.

The counts/minute for the duplicate controls and the duplicate assays of the samples containing IgE using polyclonal antibody and monoclonal antibody are shown in Tables I and II, respectively. These data were used to prepare FIGS. I and II in the following way. The average of the counts/minute for a control for a given incubation period was subtracted from the average of the counts for the corresponding IgE assay. The difference was calculated as a percentage of the total counts/minute of labelled antibody added to the sample and is plotted on the Y axis as the percentage of total counts/minute of antibody bound to the solid phase. The incubation time is plotted on the X axis.

A comparison of the plots shown in FIG. 2 displaying the results of assays using monoclonal antibody with those of FIG. 1

of assays using polyclonal antibody shows that in each kind of assay, simultaneous, reverse, forward, and fast forward, the assay using monoclonal antibody was more sensitive as indicated by the higher percentage of total counts bound to the solid phase with 100 IU IgE/ml specimen. Unexpectedly, in the case of the simultaneous and reverse assays, we have found that those run with monoclonal antibody reach equilibrium more rapidly than does the corresponding assay using polyclonal antibody. Therefore, by using a monoclonal antibody in these procedures, the time for the assay can be reduced significantly beyond the time saving achieved by merely eliminating a washing step. In that regard, the reverse assay with monoclonal antibody reached equilibrium in less than one hour. The same assay run with polyclonal assay did not reach equilibrium until after 4 hours. Similarly, in the case of simultaneous assays, the assay using monoclonal antibody reached equilibrium within 8 hours whereas the assay with polyclonal antibody did not reach equilibrium within 24 hours. Accordingly, the present invention substantially provides more rapid and sensitive simultaneous and reverse assays than the prior art processes and eliminates the concern that formation of a soluble "sandwich" complex will compete with formation of the desired insoluble complex.

The examples described above using monoclonal antibody to assay for IgE is merely one exemplar of the use of the present invention. That variations in the actual processes described in the example will be useful will be apparent to those skilled in the art. Therefore, the present invention is to be considered limited only by the appended claims.

TABLE I

Assay Results Using Polyclonal Antibody

Incubation Time (Hrs)	Simultaneous Assay		Reverse Assay		Forward Assay		Fast Forward Assay	
	Control Samples	IgE Samples	Control Samples	IgE Samples	Control Samples	IgE Samples	Control Samples	IgE Samples
0.25	372,314	2705,2667	302,243	2568,2581	357,326	2092,2077	396,293	2271,2238
0.50	348,265	2391,2366	284,262	2958,2999	288,233	1905,1817	—,—	—,—
1.00	315,277	2793,2708	305,277	3154,3218	355,424	2157,2255	304,284	1789,1706
2.00	342,356	2897,2887	290,274	3377,3212	302,314	1946,2019	288,312	1728,1867
4.00	421,385	3696,3746	28,280	3413,3651	274,255	2019,2392	283,292	1720,1683
6.00	447,436	4028,4101	296,281	3762,3643	241,267	1750,1452	301,257	1283,1424
24.00	526,577	4564,4628	233,263	3651,3546	320,277	1553,1604	273,256	1450,1470

TABLE II

Assay Results Using Monoclonal Antibody

Incubation Time (Hrs)	Simultaneous Assay		Reverse Assay		Forward Assay		Fast Forward Assay	
	Control Samples	IgE Samples	Control Samples	IgE Samples	Control Samples	IgE Samples	Control Samples	IgE Samples
0.25	135,132	5610,5803	388,594	8407,8358	210,205	4618,4894	194,183	4859,4906
0.50	558,459	7472,7115	240,231	8238,8271	223,228	4987,5273	198,197	5024,5152
1.00	268,265	6289,6529	325,265	8010,8377	230,187	3454,4308	215,192	4887,4901
2.00	282,275	6787,6784	255,302	7856,7644	226,197	4834,4268	192,210	4937,4944
4.00	308,272	8150,8155	343,305	8017,7788	231,216	5269,4420	218,187	4929,5071
8.00	549,667	8884,9494	698,850	7870,7358	226,361	2006,3631	405,243	3033,3713
25.55	426,420	8669,9044	497,323	7037,7359	194,201	2465,2586	246,233	3945,2943

We claim:

1. A process for the determination of the presence of concentration of an antigenic substance in a fluid comprising the steps:

(a) contacting a sample of the fluid with a measured amount of a soluble first monoclonal antibody to the antigenic substance in order to form a soluble complex of the antibody and antigenic substance present in said sample, said first monoclonal antibody being labelled;

(b) contacting the soluble complex with a second monoclonal antibody to the antigenic substance, said second monoclonal antibody being bound to a solid carrier, said solid carrier being insoluble in said fluid, in order to form an insoluble complex of said first monoclonal antibody, said antigenic substance and said second monoclonal antibody bound to said solid carrier;

(c) separating said solid carrier from the fluid sample and unreacted labelled antibody;

(d) measuring either the amount of labelled antibody associated with the solid carrier or the amount of unreacted labelled antibody; and

(e) relating the amount of labelled antibody measured with the amount of labelled antibody measured for a control sample prepared in accordance with steps (a)–(d), said control sample being known to be free of said antigenic substance, to determine the presence of antigenic substance in said fluid sample, or relating the amount of labelled antibody measured with the amount of labelled antibody

measured for samples containing known amounts of antigenic substance prepared in accordance with steps (a)-(d) to determine the concentration of antigenic substance in said fluid sample, the first and second monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole.

2. A process according to claim 1 wherein said first monoclonal antibody is the product of a different cell line than said second monoclonal antibody.

3. A process according to claim 1 wherein said antigen has at least two identical binding sites and said first and second monoclonal antibodies are the product of the same cell line.

4. A process according to claims 1, 2 or 3 wherein the affinity is at least about 10^9 liters/mole.

5. A process according to any of claims 1, 2 or 3 wherein said solid carrier resulting from step (d) is washed to separate the fluid sample from the carrier.

6. A process according to claim 5 wherein the solid carrier is washed with phosphate buffered saline.

7. A process according to claims 1, 2 or 3 wherein the antigenic substance is selected from the group consisting of IgE, hepatitis A, hepatitis B, hepatitis Non A/Non B, alpha-fetoprotein, carcinoembryonic antigen, insulin and human thyroid stimulating hormone.

8. A process according to claims 1, 2 or 3 wherein the labelled antibody is labelled with a member selected from the group consisting of a radioactive isotope, an enzyme and a fluorogenic material and said examination is by means selected from the group consisting of radiometric means, enzymatic means and fluorometric means.

9. A process according to claim 8 wherein said label is the radioactive isotope ^{125}I.

10. A process for the determination of the presence of an antigenic substance in a fluid comprising the steps:

(a) simultaneously contacting a sample of the fluid with first and second monoclonal antibodies to said antigenic substance, each monoclonal antibody having an affinity for the antigenic substance of at least about 10^8 liters/mole, said first monoclonal antibody being labelled and soluble in said fluid and being provided for in a measured amount and said second monoclonal antibody being bound to a solid carrier insoluble in said fluid, in order to form an insoluble complex of said first monoclonal antibody, said antigenic substance and said second antibody;

(b) separating said solid carrier from the fluid sample and unreacted labelled antibody;

(c) measuring either the amount of labelled antibody associated with the solid carrier or the amount of unreacted labelled antibody; and

(d) relating the amount of labelled antibody measured with the amount of labelled antibody measured for a control sample prepared in accordance with steps (a)-(c), said control sample being known to be free of said antigenic substance, to determine the presence of antigenic substance in said fluid sample, or relating the amount of labelled antibody measured with the amount of labelled antibody measured for samples containing known amounts of antigenic substance prepared in accordance with steps (a)-(d) to determine the concentration of antigenic substance in said fluid sample.

11. A process according to claim 10 wherein said first monoclonal antibody is the product of a different cell line than said second monoclonal antibody.

12. A process according to claim 10 wherein said antigenic substance has at least two identical binding sites and said first and second monoclonal antibodies are the product of the same cell line.

13. A process according to claims 10, 11 or 12 wherein the affinity is at least about 10^9 liters/mole.

14. A process according to any of claims 10, 11 or 12 wherein said solid carrier resulting from step (b) is washed to separate the fluid sample from the carrier.

15. A process according to claim 14 wherein the solid carrier is washed with phosphate buffered saline.

16. A process according to claims 10, 11 or 12 wherein the antigenic substance is selected from the group consisting of IgE, hepatitis A, hepatitis B, hepatitis Non A/Non B, alpha-fetoprotein, carcinoembryonic antigen, insulin and human thyroid stimulating hormone.

17. A process according to claims 10, 11 or 12 wherein the labelled antibody is labelled with a member selected from the group consisting of a radioactive isotope, an enzyme and a fluorogenic material and said examination is by means selected from the group consisting of radiometric means, enzymatic means and fluorometric means.

18. A process according to claim 17 wherein said label is the radioactive isotope ^{125}I.

19. In an immunometric assay to determine the presence or concentration of an antigenic substance in a sample of a fluid comprising forming a ternary complex of a first labelled antibody, said antigenic substance, and a second antibody said second antibody being bound to a solid carrier insoluble in said fluid wherein the presence of the antigenic substance in the samples is determined by measuring either the amount of labelled antibody bound to the solid carrier or the amount of unreacted labelled antibody, the improvement comprising employing monoclonal antibodies having an affinity for the antigenic substance of at least about 10^8 liters/mole for each of said labelled antibody and said antibody bound to a solid carrier.

20. A process according to claim 19 wherein the fluid sample is first contacted with the second monoclonal antibody to form a binary complex of the antigenic substance and said second monoclonal antibody insoluble in the fluid and then contacted with said first labelled monoclonal antibody to form the ternary complex.

21. A process according to claim 19 where in the fluid sample is first contacted with the second monoclonal antibody to form a binary complex of the antigenic substance and said second monoclonal antibody insoluble in the fluid; the sample separated from the solid carrier and the solid carrier contacted with a solution of said first labelled monoclonal antibody to form said ternary complex.

22. A process according to claim 21 wherein said solid carrier after formation of the ternary complex is washed to separate the fluid sample from the carrier.

23. A process according to claim 22 wherein the solid carrier is washed with phosphate buffered saline.

24. A process according to claims 19, 20 or 21 wherein said first monoclonal antibody is the product of a different cell line than said second monoclonal antibody.

25. A process according to claims 19, 20 or 21 wherein said antigen has at least two identical binding sites and said first and second monoclonal antibodies are the product of the same cell line.

26. A process according to claims 19, 20 or 21 wherein the affinity is at least about 10^9 liters/mole.

27. A process according to claims 19, 20 or 21 wherein the antigen is selected from the group consisting of IgE, hepatitis A, hepatitis B, hepatitis None A/Non B, alphafetoprotein, carcinoembryonic antigen, insulin and human thyroid stimulating hormone.

28. A process according to claims 19, 20 or 21 wherein the labelled antibody is labelled with a member selected from the group consisting of a radioactive isotope, an enzyme and a fluorogenic material.

29. A process according to claim 28 wherein said label is the radioactive isotope ^{125}I.

* * * * *

Appendix H

District Court, N.D. California

Hybritech, Inc. v. Monoclonal Antibodies, Inc.

No. C-84-0930

Decided August 28, 1985

PATENTS

1. Patentability—In general (§ 51.01)

Claimed assay process using monoclonal antibodies is invalid, in view of prior publications, inventions, and teachings, and in view of evidence demonstrating that its commercial success bore no causal relationship to invention, that patent teaches nothing new in art, that art alleged to be taught was obvious and logical to anyone skilled in the field, that patent fails to disclose best mode, that it fails to teach critical limitation of how to measure affinity, and that its claims are indefinite and do not disclose how infringement may be avoided.

Particular patents—Assays

4,376,110, David and Green, Immunometric Assays Using Monoclonal Antibodies, invalid.

Action by Hybritech, Incorporated, against Monoclonal Antibodies, Inc., for patent infringement. Judgment for defendant.

Lyon & Lyon, Los Angeles, Calif., for plaintiff.

Cartwright, Sucherman & Slobodin, and Flehr, Hohbach, Test, Albritton & Herbert, both of San Francisco, Calif., for defendant.

Conti, District Judge.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

This case came on regularly for trial on the 5th day of August, 1985, without a jury, and the trial consumed fifteen days. Plaintiff was represented by Lyon & Lyon of Los Angeles, California, and

defendant was represented by Cartweight, Sucherman, & Slobodin, and Flehr, Hohbach, Test, Albritton & Herbert, of San Francisco, California.

The following exposition and later contents herein are all to be considered the court's Findings of Fact and Conclusions of Law.

The Parties

*This is a suit by plaintiff Hybritech, Inc. for alleged infringement by defendant Monoclonal Antibodies, Inc. of U.S. Patent No. 4,376,110, entitled "Immunometric Assays Using Monoclonal Antibodies," issued March 8, 1983, to Gary S. David and Howard E. Greene, on application filed August 4, 1980 (hereinafter referred to as the "'110" patent). The plaintiff, Hybritech, commenced its operations in 1979, and the defendant, Monoclonal Antibodies, Inc, (hereinafter sometimes referred to as MAB) also commenced its operations in 1979; both companies are involved in the development, production and sale of diagnostic kits. While the plaintiff markets a broad range of these kits, defendant's kits are limited for pregnancy and ovulation.

The Patent in Suit

The patent in suit is directed to an alleged invention by Dr. Gary David, an immunochemist, and Ted Greene, a science graduate who has worked in management, relating to the development of diagnostic products.

The patent in suit concerns the use of monoclonal antibodies in sandwich assays. Monoclonal antibodies are genetically engineered cells called "hybridomas". These hybridoma cells are produced by fusing mouse spleen cells and malignant mouse cells (called Myelomas). The said patent, cells and assays will be more fully discussed hereinafter.

The invention is a process for determining the presence of, or the amount of, antigen in a fluid sample, such as a patient's blood or urine. An antigen is a substance, usually a protein or carbohydrate, that when introduced into the body stimulates the production of an antibody. One example of an antigen is a foreign substance in the body which causes disease, such as a virus.

Another is a substance which evidences a condition of the body. For example, the antigen IgE (immunoglobulin E) is an indication of an allergy condition; the antigen CEA (Carcinoembryonic Antigen) is an indication of colon cancer, and the antigen hCG (human Chorionic Gonadotropin) is an indication of pregnancy. Generally, an antibody may be defined as a substance produced by the body's immune system in response to the presence of a foreign antigen.

The invention of the patent, sometimes called a "sandwich" or "two-site" assay, is a method of analyzing fluids for antigens, employing certain antibodies called "monoclonal antibodies", and taking advantage of their unique properties to obtain an extremely fast, sensitive and accurate analysis. The key issue in this case is whether the defendant has overcome the presumption of non-obviousness.

The subject matter of this patent deals principally with the medical field of immunology, i.e., the workings of the body's immune system.

One of the miraculous processes of the body is its immune system. Each cell in the body has a distinct shape on its surface that distinguishes it from foreign cells. The body's army, its immune system, controls unfamiliar shapes using special troops made in the bone marrow. Certain blood or plasma cells known as lymphocytes learn to recognize the foreign molecular structure of the foreign cell or substance known as the antigen and produce antibodies which lock on to the antigen. The antigen or harmful foreign substance which "raises" the antibody is then rendered harmless in various ways. The antibody/antigen reaction is still not well understood by scientists but it may be thought of as a lock and key fitting arrangement. An antibody at its reactive site is a shape which fits and locks onto a corresponding site on the antigen known as an epitope.

The body has millions of different kinds of lymphocytes each capable of producing an antibody of a very particular structure for the purpose of seeking out a single epitope on an antigen. Once the body is invaded by an antigen a lymphocyte which produces an antibody specific for that antigen will reproduce or clone itself

in vast numbers so that a large supply of antibodies to conquer the invader may be produced. These antibodies will be specific for a particular epitope on the antigen. These antibodies being of identical molecular structure, all being made of the same clones, may be termed monoclonal antibodies. However, in the body of an animal, even though monoclonal antibodies are produced by the animal, they are always found together with other antibodies. Therefore, when the blood or serum of an animal is taken for its antibodies, the mixture found is known as "polyclonal antibodies" because it is derived from different (poly)-clones.

Introduction of an antigen into the body is termed "immunization" because it stimulates production of polyclonal antibodies which can cause immunity to the infection caused by that antigen. Most antigens are also complex and have a large number of distinct epitopes. One characteristic of an antibody is its specificity or ability to bind to a particular epitope. Another characteristic is sensitivity, defined as the smallest amount of antigen that can be detected by the antibody. Sensitivity is related to a theoretical characteristic known as affinity, which is a measure of the binding strength of an antibody for its antigen. While affinity calculations can be made for simple or small molecules, it is very difficult to do for large, complex molecules involving extremely complex reactions and can only be estimated. Also, the affinity estimations vary to a significant extent, depending upon the conditions of experiments used for the estimations.

Although the polyclonal antibodies were and are effective tools for use in immunoassay, they had certain disadvantages. If the animal died, the source of antibodies was gone and no one knew how antibodies from a different animal would compare. Also, the immune system of the animal could suddenly change the type of antibody being produced. Thus, supply of antibodies was limited and uncertain.

Since it was known that the body produced "monoclonal antibodies" within the body or "in vivo", scientists knew that if they could produce these monoclonal antibodies outside of the body or "in vitro", these problems and others would be solved. However, the plasma cells making the antibodies would not live outside of the animal and the concept of large scale production of

monoclonal antibodies was only a dream until Kohler and Milstein produced their classic paper in 1975 based on a discovery they had made on how to produce monoclonal antibodies. For this work, Kohler and Milstein in 1984 received a* Nobel prize.

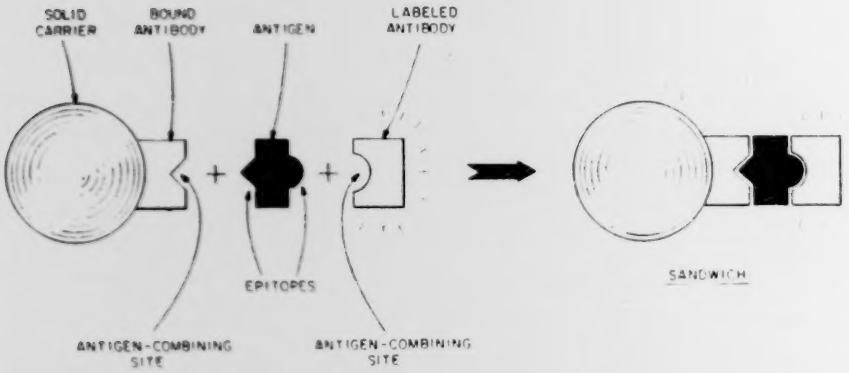
Georges Kohler and Cesar Milstein took a tumor consisting of cancer cells which grew in vitro and* fused them with normal antibody producing cells. The fusion resulted in what is called a hybridoma cell. These hybridoma cells could survive, and be cultured in vitro. Through the use of other techniques, the individual hybridoma cells could be segregated and the segregated individual cells could be cloned. These clones produce antibody molecules of identical structure or monoclonal antibodies. Suddenly, it became possible to produce tailormade, highly specific monoclonal antibodies in vast quantities. The obvious uses for diagnostic purposes of these monoclonal antibodies* became evident to those in the scientific and commercial world.

Two well-known diagnostic assay procedures using polyclonal antibodies in the prior art included "competitive assays" and "sandwich assays". In a competitive assay for an antigen in a sample, a known quantity of the same antigen is labelled. In a competitive assay for an antigen, the limited amount of antibody is bound to a solid surface. The sample containing an unknown amount of antigen is contacted with the antibody together with a known amount of labelled antigen. The labelled antigen will "compete" with any unlabelled antigen to react with the bound antibody. If there is no antigen in the test sample, all of the antigen attached to the antibody will be labelled. The greater the amount of antigen in the test sample, the less the amount of labelled antigen there will be detected. Since only a limited amount of antibody is required, this competitive test was popular with polyclonal antibodies because of the difficulty of obtaining large amount of antibodies.

In one form of the sandwich assay for the antigen, a large amount of antibody is bound to the solid surface and it is exposed to the test sample containing the unknown amount of antigen. If antigen with epitopes recognized by the antibody is present, it should bind to the antibody on the solid surface. At that point, labelled antibody, also in excess amount, is added to the solution.

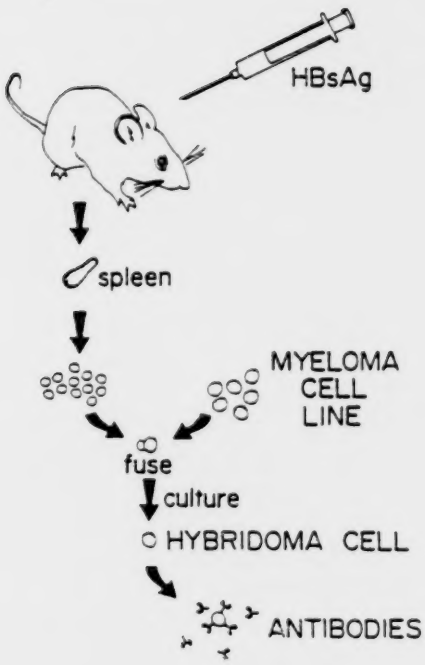
The labelled antibody will now bind to an epitope on another part of the antigen, thus the formation of a sandwich. See Figure 1. If all the reagents, i.e., reacting materials, antibodies and antigen, are added at the same time, it would be termed a simultaneous sandwich assay. All of this was known to the prior art.

FIGURE 1—SANDWICH ASSAY



People working in immunology aware of the Kohler and Milstein discovery, knew that monoclonal antibodies could be used in place of polyclonal antibodies in virtually every use to which the polyclonal had been put, e.g., monoclonal antibodies in a sandwich assay. While the idea was a simple one, putting it into practice was time consumming, and expensive, because of the steps necessary to produce the monoclonals for commercial diagnostic purposes. There are a number of complex steps* to be gone through before such kit would be available. Suitable screening assays must be developed to select the best antibody-producing clones from perhaps hundreds of thousands of them. The sheer work and time involved in "cell forming" is also considerable.

The following is a schematic illustration of hybridoma formation. Monoclonal antibody is produced against hepatitis B surface antigen (Hbs-Ag).



It was not too long before various entrepreneurs in this country decided that this technology would be worth exploiting.* While the concept, e.g., of using monoclonal antibodies in a sandwich assay was simple and obvious, the work and technology involved in coming up with the right antibody, testing for it, finding economically feasible ways to attach antibody to solid surface to label antibody, would be difficult and expensive.*

A* Stanford MBA, named Thomas Glaze, decided in the summer of 1978 that he would form a company (the defendant company herein) to produce monoclonal antibodies to replace polyclonal antibodies in diagnostics. Mr. Glaze, as evidenced by his business plan, intended to contact certain customers who were using sandwich assays with polyclonal antibodies.* The defendant Monoclonal Antibodies, Inc. (MAB) was formed in April 1979. The evidence indicated* discussions in the fall of 1979 involving the use of monoclonal antibodies in sandwich assays. In March of 1980, MAB began selling monoclonals and informed others, both

orally and in writing, that sandwich assays were included among their potential uses. Plaintiff's patent application was not filed until August 4, 1980, and the patent did not issue until March 8, 1983. Without any knowledge of the activities at Hybritech, MAB on its own, developed commercial kits using monoclonal antibodies in sandwich assays. After obtaining government approval, MAB, in November of 1982, had a kit on the market.

An experienced marketing manager with an MBA from Harvard, named Ted Greene, had similar ideas. He was brought in in early 1979 to become president and chief executive officer of Hybritech, Inc. (Hybritech), a company which had been formed a few months earlier, also to develop monoclonal antibodies to be used in place of polyclonals. While the Hybritech people* had considered the various uses to which the new monoclonal antibody tool could be put, one of which was in assays such as a sandwich assay, they had not yet* decided exactly what they would be doing regarding monoclonal antibodies in diagnostics. They did, however, know that they were going to develop monoclonal antibodies antigens and they began to do so. At no time before May of 1980, is there any documentation whatsoever which even suggests that the idea at Hybritech of using monoclonal antibodies in sandwich assays would be innovative. Nor is there any clear or corroborated testimony with regard to when before May of 1980, the idea of actually using monoclonals in sandwich assays was first discussed.

During the time frame in question, at least five different groups of workers in the field employed sandwich assays using monoclonal antibodies. For example, at La Jolla Cancer Research Foundation (LJCRF) a team of scientists headed by Dr. Ruoslahti and including Drs. Engvall and Dr. Uotila, developed and ran a simultaneous sandwich assay using monoclonal antibodies. Laboratorynotebooks proved this was done no later than November 5, 1979. This work was submitted to two respected scientific journals and published in November of 1980 in the Journal of Immunological Methods. At the exact same time that this work was going on, Hybritech, then a fairly small company, had its offices and shared space and equipment with LJCRF.

As early as July 1978, and merely because monoclonal antibodies were available at the Stanford University Laboratory of Dr. Herzenberg, a sandwich assay using monoclonal antibodies was performed. This work was published in December 1979, in a Journal called Molecular Immunology. The sandwich assay was one of a series of diagnostic procedures set forth by Dr. Herzenberg, who did not single out the sandwich assay as anything out of the ordinary.

Hybritech, by the spring of 1980, had raised many millions of dollars with the backing of venture capitalists. They were thus able to afford and hire a* man of vast experience in diagnostics and patents by the name of Dr. Thomas Adams. This was done in April 1979.

One of the first things Adams wanted to know as an executive of Hybritech was what subject matter there was* that the company could patent. In a memorandum to Greene on April 25, 1980, re "patentable ideas", Adams, after setting forth a few ideas stated:

> Also can we try for a general patent on the use of labelled monoclonal Ab [antibody] or coating with monoclonals if we can show meaningful advantages over conventional antiserum?

As of April 25, 1980, even though they discussed patentable ideas, there is no mention of the subject matter of the patent in suit. Dr. Adams then decreed that every technical worker at Hybritech should have an idea notebook. On April 28, Dr. Gary David, Hybritech's chief scientist, wrote a number of entries in his "idea notebook", none of which included the subject matter in question.* May 6 is his first entry which suggests only that the simultaneous assay using monoclonal antibodies is new. In the same month, experiments were* carried out, so that now Hybritech had* reached the point where they, too, had run a simultaneous sandwich assay using monoclonal antibodies.*

In the first review of the patent application by the U.S. Patent and Trademark Office (PTO), the Patent Examiner rejected all of the originally filed claims as being obvious under Section 103 of the patent statute (35 U.S.C. § 103) in view of the Cuello prior

art reference, alone or in combination with other prior art references. The Cuello reference disclosed using monoclonal antibodies in an immunoassay and the other references disclosed sandwich assays using polyclonal antibodies. The Examiner pointed out that Hybritech's application conceded that the sandwich assay protocols of the claim are old and concluded " . . . it would be obvious to use the monoclonal antibody for the polyclonal antibodies in the conventional immunoassay protocols defined by the instant claims . . . "

As* hereinabove noted, competitive and sandwich assays are similar. In Cuello, monoclonal antibodies were used in a competitive type assay.

Hybritech's attorney argued that based upon the differences between a competitive and a sandwich assay, it would not be obvious to use the monoclonal antibodies of Cuello in the sandwich assay. The Examiner was not convinced by the Arguments, and again (the second time) rejected the claims on grounds similar to the first rejection.

*Hybritech's attorney then amended the broadest claims to include a numerical limitation (at least 10^8 liters/mole) regarding the affinity (strength of binding) of the antibodies to corresponding antigen and restated his arguments. Hybritech's attorney supported his argument with a declaration from Richard Bartholomew, a Hybritech employee, alleging certain advantages of using monoclonal antibodies rather than polyclonal antibodies in sandwich assays.

It is obvious that in order to perform in a sandwich assay, the antibodies have to be of high affinity. Hybritech used 10^8 liters/mole as the arbitrary cutoff point in their selection of antibodies for further testing during the antibody development phase. It was well known that high affinity antibodies were required for these assays in the prior art.*

The so-called reasons for allowance were not well-founded because (1) the alleged advantages were expected as naturally flowing from the well-known natural characteristics of monoclonal antibodies compared to polyclonal antibodies; (2) alleged advantages were not significant but argued to the Examiner

as if they were; or (3) were at best minor advantages of certain monoclonal antibody sandwich assays and not applicable to all monoclonal antibodies as claimed by Hybritech.

The credible testimony of J. Blakemore indicated that the reasons for the final granting of the patent by the Examiner were not scientifically valid and misplaced.*

It is of the utmost importance to be aware that shortly after Kohler and Milstein's discovery made monoclonal antibodies known and they became available, their advantageous use in various immunoassays was predicted by a number of authorities,* none cited by the Patent Office.

A 1978 edition of Cellular Immunology, in a chapter relating to monoclonal antibodies, Drs. Herzenberg and Milstein, is stated at page 25.1: "Apparently inexhaustible supplies of pure, specific, standardized antibody can now be assured for almost any clinical or laboratory immunoassay."

In January 1979, in Chemical and Engineering News, is stated: " . . . [A]dapting monoclonal antibodies to radioimmunoassay [immunoassays using radioactive labels] that are widely used in clinical tests is a predictable, potentially important development . . . "

In early March, 1980, in Nature, in an article dealing with immunomertric or sandwich assays, Dr. Ekins stated: " . . . Combined in the exploitation of the in vitro hybridoma techniques of antibody production pioneered by . . [Kohler and Milstein] . . . with which large quantities of monospecific antibodies can be produced, the emergence of simple and reliable assay procedures far surpassed current . . [competitive assays] . . in sensitivity, precision, speed, specificity and overall reliability is within sight . . . "

In his February 1980 article in Clinical Microbiology Newsletter, Dr. Sevier of Hybritech, stated under the hearing "Uses in Immunoassay: "An essentially unlimited supply of monoclonal antibodies, precisely defined according to amount and affinity, will lead to major improvements and innovations in immunochemical techniques. For immunodiagnostics, monoclonal antibodies will improve performance, reduce costs and open up types of immuno-

logical testing. More obvious advances will include. . . . Antibodies for use with . . . enzyme . . . immunoassays . . . "

Furthermore, as conceded by Hybritech, the sandwich assay procedures using polyclonal antibodies were well known in the orders of addition of antibody to antigen of the patent in suit. (See, e.g., the simultaneous assay of the Jeong patent 4,244,940).

In addition, monoclonal antibodies of affinity in excess of 10^9 liters/mole were known (Frankel and Gerhard article in Molecular Immunology, DX.AB),* as was the desirability of polyclonal antibodies of such affinity in immunoassays, including sandwich assays.

In December, 1979, Oi and Herzenberg published an article in Molecular Immunology disclosing the use of monoclonal antibodies in a sandwich assay based upon work performed in 1978 and submitted for publication in April 1979. The article refers to the subject matter of the patent in suit merely as a modification of a radioimmunoassay, i.e., other well-known technology.

**Authority Regarding Validity*

A. *Obviousness:*

Section 103 provides as follows:

> A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. . . .

The Patent Examiner felt the subject matter was obvious and only changed his mind in reliance on the* Bartholomew Declaration. He did not have available the various references* noted before. The trial testimony of experts indicate the bases for the issuance of the patent by the Examiner was incorrect. (See testimony of J. Blakemore).

In view of the foregoing, it would be obvious to substitute in a known sandwich assay, known high affinity monoclonal antibodies for polyclonal antibodies of similar affinity for the known advan-

tages of monoclonal antibodies over polyclonal antibodies in immunoassays.*

B. *Prior Invention of Others*

Plaintiff's patent is invalid under 35 U.S.C. § 102(g):

> "... before the applicant's invention thereof the invention was made in this country by another who has not abandoned, suppressed, or concealed it."

Based on the above facts, the simultaneous sandwich assay using high affinity monoclonal antibodies (greater than 10^9 liters/mole) was reduced to practice by LJCRF in the United States as early as November, 1979, long prior to the August 4, 1980 filing date of the '110 patent. LJCRF continued the work on the project by conducting further experiments, and preparing papers and patent applications which ultimately were filed and published. Even if such reduction to practice were secret, it would invalidate the patent if the invention was not abandoned, suppressed or concealed.* LJCRF did not abandon, suppress or conceal since steps were taken to make the invention publicly known and it diligently pursued publication and filed a patent application.* Therefore, the Foundation's reduction to practice constitutes prior art under 35 U.S.C. § 102(g) and is prior art at least as early as November 5, 1979.

The same is also true for the work of Oi and Herzenberg, where the reduction to practice took place in July of 1978.*

Hybritech did not establish an earlier date of invention than the above two mentioned references since there is no credible evidence of conception prior to May of 1980.*

C. *Invalidity under 35 U.S.C. § 112*

The limitation of an affinity for the antigen of at least about 10^8 liters/mole is present in all of the '110 patent claims, and was added by amendment during prosecution in response to the first rejection by the Examiner. Also, the affinity limitation was cited by the Examiner as a reason for allowance. In spite of this significance attributed to it during prosecution, the specification fails to teach how to obtain monoclonal antibodies having such

affinities or why the limitation is significant. The first paragraph of Section 112 requires a written description of the invention in sufficient detail so that one can perform it. The specification fails to disclose how to measure affinities (if they can be "measured" rather than merely estimated). Also, or fails to disclose whether affinity is determined (1) when the antobidies are in their natural form as produced by the hybridoma, or (2) after the antibodies are either bound to the support surface or attached to the labelled antibody.

The first paragraph of Section 112 also requires applicant to set forth the best mode contemplated by the inventor for carrying out his invention. However, the specification fails to disclose how to form and screen the many hybridoma cells lines to identify those hybridoma that produce antibodies having the specified affinities.*

Under the second paragraph of Section 112, the claims must particularly point out and distinctly claim the invention. As discussed above, the specification of the '110 patent does not disclose any method for determining the affinities of monclonal antibodies. The definiteness requirement of § 112 is not met if the patent does not disclose to the public how infringement may be avoided. *Norton Company v. Bendix Corporation*, 449 F.2d 553, 555, 171 USPO 449, 450 (2d Cir. 1971). Since the antibody affinity was inserted as a limitation in all of the broadest (independent) claims of the '110 patent and argued by Hybritech to be a critical limitation, those of ordinary skill in the art must be able to determine this number with certainty in order to determine whether they are infringing. There is no standard set of experimental conditions which are used to estimate affinities and the variations in the values which are estimated.*

The court, in reaching its conclusion that the patent in issue is invalid, is persuaded by the credible testimony of Dr. Vernon Oi, Judy Blakemore, Thomas Ciotti, Dr. Scott Monroe, Dr. Leonard Hertzenberg, Dr. Ruoslahti, and Dr. Amshey.

Laughton Miles in the late 1960's made known the sandwich assay with the use of monoclonal antibodies.

Kohler and Milstein gave the know-how for the development of monoclonal antibodies.

All of the modes of assay were known by the prior art. The testing kits and procedure prior to Kohler and Milstein used polyclonal antibodies, and once Kohler and Milstein invented the technology for developing monoclonal antibodies, it was obvious to use monoclonal antibodies in a sandwich assay where polyclonal antibodies had been used in the past.

The testimony of plaintiff's own witness and co-inventor of the patent in suit, in discussing the key elements of the patent, stated: the patent states that you need antibodies with high affinity—yet he says this was known in the prior art. Also, he (David) says you need remote sites on the antigen, however, a sandwich assay to work well must have remote sites—this is obvious, and yet the patent does not tell you how to do this—David went on to state that this was known in the literature. In sum, you screen till you get two antibodies that work in an assay.

Even the witness for plaintiff, Dr. Nisonoff, stated that "once monoclonal antibodies were known it would be logical and expected that monoclonal antibodies would reach equilibrium faster because of the known physical properties of monoclonal antibodies, and if you were working with monoclonal antibodies you would consider their affinity when thinking of diagnostic uses.

Dr. L. Hertzenberg, Ph.D, and with a world-wide reputation, and who worked in the Milstein laboratory in England, stated that in 1977 he did a sandwich assay with monoclonal antibodies. Hertzenberg stated that the monoclonal assay was obvious.

It is the court's conclusion that the major advance was the invention of Kohler and Milstein in the making of monoclonal antibodies, that is the ability to clone a cell to the properties you want and to have that clone cell live forever.

Once the scientific community had the monoclonal antibody it was obvious and logical to those experts in the field to use them in known assays as substitutes for products (polyclonal antibodies) of inferior qualities.

The plaintiff has not sustained the burden of proof with the requisite corroborative evidence as to the "date of conception" or the date of "Reduction to Practice".

The court further finds that plaintiff's contention to rebut obviousness, to wit; the commercial success of the kits re the patent in suit, is unpersuasive. Commercial success, to be meaningful indicia of unobviousness, must be related directly to the claimed inventions. Here the court finds that the commercial success of the kits may well be attributed to the business expertise and acumen of the plaintiff's personnel, together with its capital base and marketing abilities. Business success is not the ultimate criteria for unobviousness.

The defendant has not been able to sustain its burden of proof re inequitable conduct on the part of the defendant.

The matter of infringement is moot, as the court finds the patent in issue invalid.

The court makes further findings of fact and conclusions of law, even though some of the following findings and conclusions are repetitive to the foregoing, for the sake of completeness and to give due reference to the facts that the court has found.

1. Plaintiff, Hybritech, Inc. (hereinafter "Hybritech") is a corporation organized and existing under the laws of the State of California and has its place of business at 11085 Torreyana Road, San Diego, California.

2. Defendant, Monoclonal Antibodies, Inc. (hereinafter "Monoclonal"), is a corporation organized and existing under the laws of the State of California and has its principal place of business at 2319 Charleston Road, Mountain View, California.

3. This is an action for infringement of U.S. Letters Patent No. 4,376,110 (hereinafter the " '110 patent").

4. The application for the '110 patent was filed August 4, 1980, and named Gary S. David and Howard E. Green as joint inventors. It issued March 8, 1983 and was assigned to Hybritech. It relates to the use of monoclonal antibodies having affinities of at least* 10^8 liters/mole in sandwich assays for detecting antigens.

The antigen is sandwiched between a bound antibody on a solid carrier and a labelled antibody. Claims 1-9 are directed to a reverse sandwich assay in which the labelled antibody is reacted with the antigen prior to contact with the bound antibody. Claims 10-18 are directed to a simultaneous sandwich assay in which the antibodies and antigen are reacted simultaneously. Claim 19 is directed to the sandwich assay without specifying the order of addition of reagents. Claims 20-29 are dependent on claim 20.*

5. As conceded by Hybritech in the patent, the use of polyclonal antibodies in sandwich assays as well known prior to the alleged invention of the '110 patent with various orders of addition of reagents, including the reverse and simultaneous mode U.S. Patent No. 4,244,940 (Defendant's Exhibit A) to Jeong, et al., issued January 13, 1981, discloses a simultaneous sandwich assay using polyclonal antibodies. U.S. Patent No. 4,098,876 to Piasio, et al., issued July 4, 1978, discloses a reverse sandwich assay using polyclonal antibodies. U.S. Patent No. 4,016,143 to Shurrs, et al., issued April 5, 1977, discloses a forward sandwich assay using polyclonal antibodies.

6. A method for producing monoclonal antibodies in virto was well known prior to the alleged invention of the '110 patent. This method was disclosed first in an August 7, 1975 publication in Nature, Vol. 256, pp. 495-497, by G. Kohler and C. Milstein entitled "Continuous Cultures of Fused Cells Secreting Antibody of Predetermined Specificity." (Testimony of Blakemore, Defendant's Exhibit AL.)

7. The existence of monoclonal antibodies having the affinity constants claimed in the '110 patent was well known prior to the alleged invention of the '110 patent. For example, monoclonal antibodies having affinities of greater than 10^8 and some greater than 10^9 liters/mole were disclosed in a February 1979 publication in Molecular Immunonology, Vol. 16, pp. 101-106 by M.E. Frankel and W. Gerhard entitled "The Rapid Determination of Binding Constance for Anti-Viral Antibodies by a Radioimmunoassay." Defendant's Exhibit AB—per Blakemore testimony.

8. The use of monoclonal antibodies in competitive assays ("RIA"), was well known prior to the alleged invention of the

'110 patent. This use was disclosed in a July 1979 publication in the proceedings of the National Academy of Science, Vol. 76, No. 7, pp. 3532-3536, by A.C. Cuello, G. Galfre and C. Milstein, entitled "Detection of Substance P in the Central Nervous System by a Monoclonal Antibody." Defendant's Exhibit V.

9. Sandwich assays using monoclonal antibodies were disclosed in a December 1979 publication in Molecular Immunology, Vol. 16, pp. 1005-1017, by V.T. Oi and L.A. Herzenberg, entitled "Localization of Murine Ig-Ib and Ib-Ia (IgG_{2a}) Allotypic Determinants Detected with Monoclonal Antibodies", long prior to the alleged invention of the '110 patent.

10. The alleged invention of the '110 patent was contemporaneously developed by at least five different groups of workers in the field and was disclosed in various patent applications and publications between the filing date and the issue date of the '110 patent. For example, European Pat. App. No. 81220768 (defendant's Exhibit G), Akzo N.V. published February 3, 1982, Bulletin 82/5; European Pat. App. No. 81302809.0 (defendant's Exhibit H), Unilever N.V., published December 30, 1981, Bulletin 82/52; European Pat. App. No. 81106832.9, La Jolla Cancer Research Foundation, published March 31, 1982, Bulletin 82/13, and P.C.T. App. P.C.T./US 81/01270 (defendant's Exhibit N), Massachusetts General Hospital, published April 1, 1982, all disclose sandwich assays using monoclonal antibodies.

11. Shortly after the Kohler and Milstein disclosure of monoclonal antibodies stated in Finding 6, the use of monoclonal antibodies in immunoassays was expected and predicted by numerous authorities and commentators in the field. For example, the following publications predicted the use of monoclonal antibodies in immunoassays:

(a) The 1978 publication in Handbook of Experimental Immunology, D. Weir, Editor, Blackwell Scientific Publications, Oxford, pp. 25.1-25.7, by* L.A. Herzenberg and C. Milstein entitled "Cell Hybrids of Myelomas with Antibody Forming Cells and T-Lymphocytes and T-Cells", states: "The recent adaptation of cell hybridization techniques to the construction of myeloma-like cell lines producing monoclonal antibodies with desired

reactivitites has essentially revolutionized the approach to production and utilization of immunospecific reagents. Apparently inexhaustible supplies of pure, specific, standardized antibody can now be assured for almost any clinical or laboratory immunoassay."

(b) The January 1979 publication in Chemical and Engineering News, Vol. 57, No. 1, by J.L. Fox entitled "Antibody Reagents Revolutionizing Immunology" states ". . . [A]dapting monoclonal antibodies to radioimmunoassays that are widely used in clinical tests is a predictable, important development . . ." (Defendant's Exhibit AA).

(c) The June 1979 publication in AJEBAK, Vol. 57, Part 3, pp. 231-344 by G.F. Mitchell et al., entiltled "Hybridoma Antibody Immunoassays for the Detection of Parasitic Infection: Development of a Model System Using a Larval Cestode Infection in Mice" states: "Monoclonal antibodies derived from antiparasite antibody-secreting hydridoma cell lines will be of particular use in the development of new, highly specific, immunodiagnostic reagents for the detection of parasite infection, exposure and disease." (Defendant's Exhibit A).

(d) The 1979 publication in Antibodies in Human Diagnosis and Therapy, E. Haber and R.M. Krause, editors, Raven Press, New York, pp. 225-236 by N.R. Klinman, G.P. Segal, W. Gerhard, T. Braciale and R. Levy, entitled "Obtaining Homogeneous Antibody of Desired Specificity from Fragment Cultures" states: "Perhaps the most obvious of antibodies of a known restricted specificity would be diagnostic." (Defendant's Exhibit AE).

(e) The winter 1979 publication in Ligand Review, Vol. 2, No. 2, by D.S. Skelly entitled "Antibodies: New Developments", states: "The use of monospecific antibodies in immunodiagnostic testing is obvious." (Defendant's Exhibit BE).

(f) The February 1980 publication in The Yale Journal of Medicine, Vol. 53, pp. 71-83 by A. Baumgarten entitled "Viral Immunodiagnosis" states ". . . The specificity and uniformity of monoclonal antibodies should markedly improve diagnostic accuracy . . ."

(g) The February 1980 publication in Clinical Microbiology Newsletter, Vol. 2, No. 3, pp. 1-2 by D.E. Sevier, an employee of plaintiff, entitled "Revolutionary Reagents: Monoclonal Antibodies from Hybridomas" states: "An essentially unlimited supply of monoclonal antibodies, precisely defined according to amount and affinity, will lead to major improvements and innovations in immuno medicine techniques. For immuno-diagnostics, monoclonal antibodies will improve performance, reduce costs and open up types of immunological testing. More obvious advances will include . . . antibodies for use with . . . enzyme . . . immunoassays . . ." (Defendant's Exhibit BB).

(h) The March 6, 1980 publication in Nature, Vol. 284, p. 14 by R. Ekins, entitled "More Sensitive Immunoassays," states "Combined with the exploitation of the in vitro hybridoma techniques of antibody production pioneered by Milstein and his colleagues at Cambridge . . . with which large quantities of monospecific antibodies can be produced, the emergence of simple and reliable assay procedures far surpassing current RIA techniques in sensitivity, precision, speed, specificity, convenience and overall reliability is within sight."

12. The prior art stated in Findings 7, 9 and 11 was not considered during prosecution of the application. This art was more pertinent than the art considered by the Examiner.

13. Any commercial success of the patent was caused by the sudden availability of a new reagent, monoclonal antibodies, together with further reasons hereinabove stated.

14. The primary advantages of monclonal-based sandwich assays are due to the inherent, known and expected properties of monoclonal antibodies. Any other advantages, expected or not, are insignificant in comparison to the primary advantages.

15. Any differences between the prior art stated in Findings, 5, 6, and 7, viewed with or without the prior art stated in Finding 11, and the the '110 patent, would been obvious to one of ordinary skill in the immunoassay art at the time the alleged invention of the '110 patent was made.

16. Any differences between the prior art stated in Findings 7 and 9, viewed with or without the prior art stated in Finding 11, and the the '110 patent, would have been obvious to one skilled in the immunoassay art at the time the alleged invention was made.

17. Any differences between the prior art stated in Findings 5, 6, 7 and 8, viewed with or without the prior art stated in Finding 11, and the the '110 patent, would have been obvious to one skilled in the immunoassay art at the time the alleged invention was made.*

18. A simultaneous sandwich assay using monoclonal antibodies having affinity constants greater than 10^9 liters/mole was reduced to practice by researchers M. Uotilla and E. Ruoslahti at La Jolla Cancer Research Foundation in the United States as early as November 1979.

19. The reduction to practice of Finding 18 resulted in the preparation and publication of an article in The Journal of Immunological Methods in 1981 by them, and the preparation and the filing of a patent application in Sweden in 1980 by Pharmacia, which was assigned to the Foundation.

20. A sandwich assay using monoclonal antibodies was reduced to practice by Vernon Oi at Stanford University in July 1978.

21. This reduction to practice of Finding 20 resulted in a publication in the Journal of Immunology in 1978 and a publication in Molecular Immunology in December 1979.

22. The reductions to practice set forth in Findings 18 and 20 were not abandoned, suppressed or concealed.*

23. The claims of the '110 patent are not limited in scope to particular antibodies or concentrations.*

24. The specification of the '110 patent fails to disclose how to measure affinities and fails to disclose whether affinity is determined (1) when the antibodies are in their natural form as produced by the hybridoma or (2) after the antibodies are either bound to the support surface or attached to the label.*

25. The specification of the '110 patent fails to disclose how to form and screen the many hybridoma cell lines resulting from cell fusion and to identify the particular hybridoma-producing antibodies having the affinities required to practice the processes claimed.*

CONCLUSIONS OF LAW

[1] 1. The '110 patent is invalid under 35 U.S.C. § 103 in view of the December 1979 publication by V.T. Oi and L. A. Herzenberg, and the February 1979 publication by M.E. Frankel and W. Gerhard, *Lear Siegler, Inc. v. Aeroquip Corp. et al.*, 733 F.2d 881, 221 USPQ 1025 (Fed. Cir. 1984); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). With respect to the secondary considerations relevant to a determination of obviousness, where the primary advantages of the invention are known and expected, unexpected other advantages cannot rebut evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 193 USPQ 641 (CCPA 1977). Finally, commercial success must be related to the claimed invention. Where commercial success is based on the sudden availability of starting materials, in this instance the availability of monoclonal antibodies as a result of the Kohler and Milstein discovery, business acumen, marketing ability, and capital sources, no causal relationship is proven. *Technograph Printed Circuits Ltd. v. United States*, 164 USPQ 584 (Comm'r. Op. Ct. Cl. 1970).

2. The said patent is invalid because it teaches nothing new in the art, the art alleged to be taught was obvious and logical to anyone skilled in the field.*

3. The '110 patent is invalid under 35 U.S.C. §§ 102(g), 103, in view of prior "inventions" and teachings.*

4. The '110 patent is invalid under 35 U.S.C. § 112, first paragraph, because it fails to disclose the best mode known to Hybritech of screening hybridomas to obtain appropriate monoclonal antibodies,* and fails to disclose the best mode known to the applicant of forming the hybridomas to be used in the production of monoclonal antibodies.*

5. The '110 patent is invalid under 35 U.S.C. § 112, first paragraph, because it fails to teach how to measure affinity and fails to disclose whether affinity is determined when the antibodies are in their natural form or after being bound to a support or attached to a label.

6. The '110 patent is invalid under 35 U.S.C. § 112, second paragraph, because the claims are indefinite; they do not disclose how infringement may be avoided because antibody affinity cannot be estimated with any consistency. *Norton Co. v. Bendix Corp.*, 449 F.2d 553, 171 USPQ 449 (2d Cir. 1971).

7. The defendant has proven patent invalidity and prior invention by clear and convincing evidence.

8. Defendant's kits do not infringe the '110 patent because* of the said patent's invalidity.

Judgment is granted in favor of defendant and against plaintiff. Defendant shall be entitled to its costs.

No. 86-1318

In the Supreme Court of the United States

October Term, 1986

MONOCLONAL ANTIBODIES, INC.,

Petitioner,

v.

HYBRITECH INCORPORATED,

Respondent.

ON PETITION FOR WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION TO PETITION FOR WRIT OF CERTIORARI

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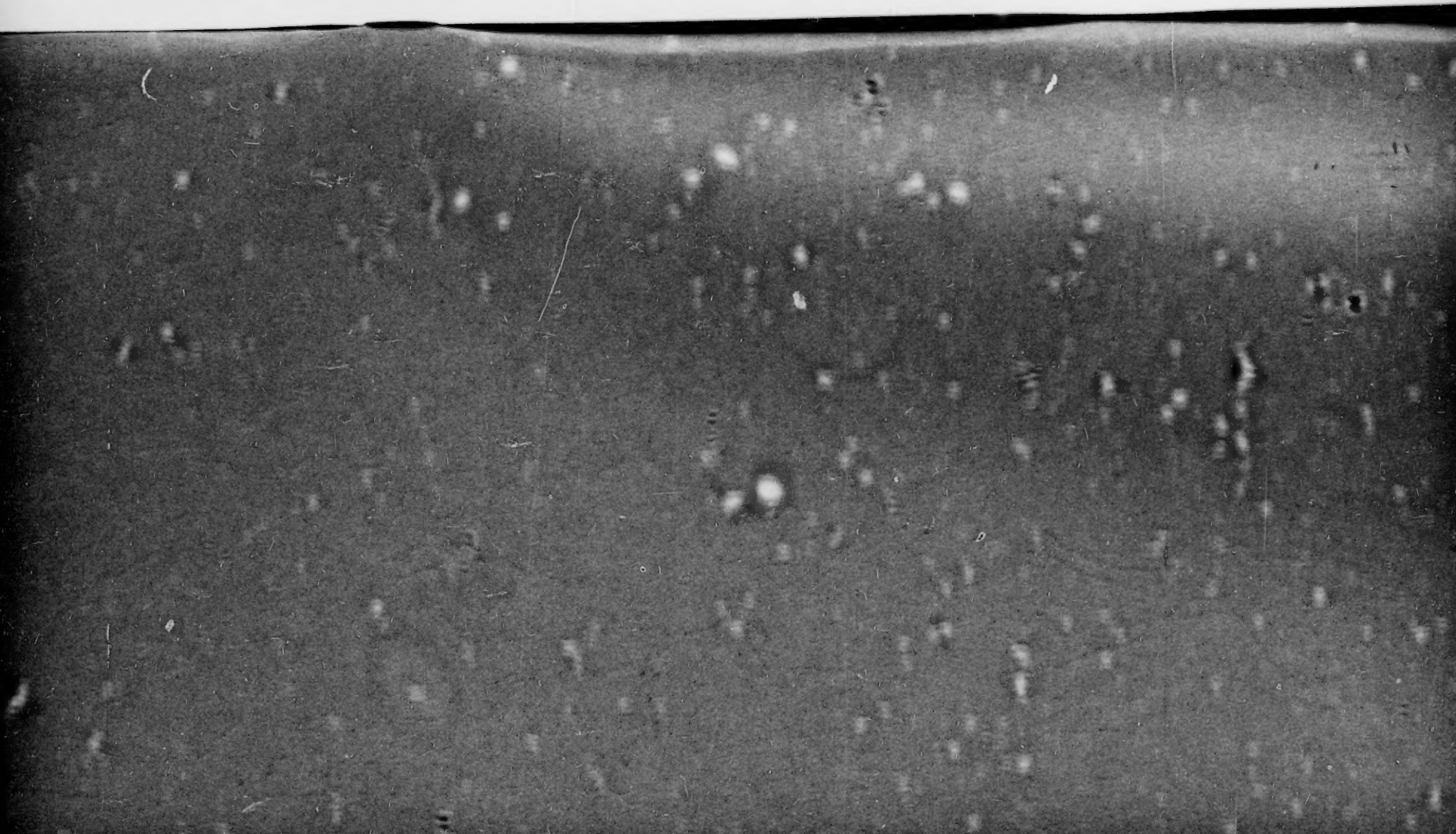

QUESTION PRESENTED

Petitioner's complaint is that the Court of Appeals for the Federal Circuit decided this patent case against it. Its Statement of Questions Presented mistakenly asserts violations of Rule 52(a) where none exist, and misreports the record to claim issues under 35 U.S.C. §103 which do not exist and to argue for an interpretation of Section 103 under which that statute is ignored. Petitioner also alleges a procedural failure that did not occur and which, even if it had occurred, would have no bearing on the outcome of this case. Restated, therefore, the sole question for which review is sought can be nothing more or less than whether the Court of Appeals for the Federal Circuit properly held that Petitioner failed to meet its burden of proving patent invalidity pursuant to 35 U.S.C. §282.

Contrary to Petitioner's opening, this case involves no Constitutional provisions. Thus, beyond the sole assertion at page 2 that the Fifth Amendment is involved, one finds no further citation or reference to it. Additionally, past that page, one finds no further substantive reference to the patent and copyright clause of the Constitution, which simply provides Congress with the power, *inter alia*, to enact patent law.

In asking the United States Supreme Court to take up this case, Petitioner requests simply that it conduct a fresh review of the voluminous records of two courts below to rule that the Federal Circuit was wrong and to reinstate all determinations of the District Court that have been held to be clearly erroneous or legally incorrect following review by a unanimous Court of Appeals.

RULE 28.1 STATEMENT

Respondent, Hybritech Incorporated, provides the following list of corporate affiliates in compliance with Rule 28.1:

Eli Lilly & Company
Gen-Probe Incorporated

TOPICAL INDEX

TABLE OF AUTHORITIES CITED

Statutes

Rules

No. 86-1318

In the Supreme Court of the United States

October Term, 1986

MONOCLONAL ANTIBODIES, INC.,

Petitioner,

v.

HYBRITECH INCORPORATED,

Respondent.

BRIEF IN OPPOSITION TO PETITION FOR WRIT OF CERTIORARI

STATEMENT OF THE CASE

As evidenced by the extensive discussion of the factual background of the invention by the Federal Circuit, it is important to understand the claimed invention and its substantial differences from and advantages over the prior art. Because Petitioner's Statement of the Case attempts to write those differences and advantages out of existence, and because of other inaccuracies and omissions, Respondent provides this Statement pursuant to Supreme Court Rule 34.2.

Respondent's invention is a very specific type of immunoassay process. At the time Respondent's

invention was made, many different types of immunoassay protocols were known (RA1).[1] Each used as the antibody reagent a polyclonal antiserum, which is a mixture of antibodies isolated from animal blood serum, directed to various antigens and to any number of epitope binding sites on a particular antigen (PA2). Contrary to Petitioner's misleading claim, polyclonal antiserum is not comprised of "monoclonal antibodies", that term being one of art to denote those antibodies produced by the hybridoma cell fusion process which was briefly described by the Court of Appeals (PA2). This cell fusion procedure was first published in 1975 so that by the time Respondent's invention was made in 1979, according to Petitioner's own expert, there were hundreds or thousands of people in the U.S. alone making monoclonal antibodies (RA2-3). Accordingly, Petitioner's contrary statements now that monoclonals were "virtually impossible" to obtain "until recently", and that this explains the previous use of polyclonal antiserum, is neither legitimate nor supported by the record (PA26-27).

Positing "significant problems" with polyclonal antisera as a prelude to the unsupported claim that "scientists knew" that monoclonal antibodies were a panacea, Petitioner concludes without citation that monoclonals "transformed the immunoassay test kit industry." Witnesses employed by Petitioner, by Respondent, and third party witnesses, however, all testified that monoclonal antibodies had significant problems believed to make their use in immunoassays undesirable. What transformed the immunoassay industry was Respondent's patented invention.

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[1]References to Respondent's Appendix are abbreviated "RA". References to Petitioner's Appendix are abbreviated "PA".

As noted, there were a wide variety of assay techniques employing antibodies at the time the invention was made. They suffered from many common problems including that they were too slow, too complicated, not sufficiently accurate, not sufficiently sensitive, and not sufficiently specific for the target antigen. Respondent's invention solved these problems, leading to unprecedented commercial success. The impact of the invention is illustrated by the fact that it converted the so-called "sandwich"-type assay from a position of distrust and little use to one of market dominance. According to Petitioner's own expert, Blakemore, of 425 immunoassays marketed in 1979 when Respondent's invention was made, over 86% used one particular format, an "exquisitely sensitive" protocol known as the "radioimmunoassay" (RIA), the inventors of which were awarded a Nobel Prize. In sharp contrast, less than 1% (three in number) used the much less sensitive sandwich assay format, which formed a starting point for the claimed invention.

Today a majority of the assays introduced into the market are sandwich-type assays using particularly defined monoclonal antibodies (PA27 n.5). The commercial impact of this invention by Respondent, a small, 1978 venture capital start-up company, is briefly summarized at PA26, where the Federal Circuit noted that Respondent swiftly became the market leader in several fields of immunoassay testing while competing against the giants of the diagnostic industry. Even Petitioner lauds Respondent's great advance in its promotional literature, heralding the invention as faster, simpler, more accurate, and more sensitive than previously known immunoassays. It is, says Petitioner, a "pioneering approach". Monoclonal Antibodies, Inc., 1985 Annual Report, Plaintiff's Trial Exhibit 646.

Reflective of the merits of Petitioner's claim that monoclonal antibodies would be useful wherever polyclonal antisera had been used and that, therefore, there could never be any patentable inventions relating thereto, is the testimony of its own experts about the significant problems of monoclonals. For example, most workers in the field believed — and many still do — that monoclonals have affinities less than conventional polyclonal antiserum and too low for use in immunoassays. Indeed, in 1982, *three years after Respondent's invention*, Petitioner saw fit to announce in its Annual Report that it had "overcome the problem of low affinity encountered by most producers of monoclonal antibodies". Monoclonal Antibodies, Inc., 1982 Annual Report, Plaintiff's Trial Exhibit 25. Petitioner's cofounder noted *in 1980 and 1982* scientific papers the low affinity "drawback" of monoclonals. J. Schroeder, *Monoclonal Antibodies: A New Tool for Research and Immunodiagnostics,* 58 Medical Biology 140 (1980), Plaintiff's Trial Exhibit 74; J. Schroeder, *Monoclonal Antibodies to Human Chorianic Gonadotropin,* (1982), Plaintiff's Trial Exhibit 81. Petitioner's own expert, Dr. Stites, taught in 1984 in the 5th edition of his treatise on clinical immunology that a disadvantage of monoclonals is "decreased affinity". D. Stites, "Clinical Laboratory Methods for Detection of Cellular Immune Function," *Basic and Clinical Immunology* (5th Ed., c.1984), Plaintiff's Trial Exhibit 718. Witnesses for both parties and third party witnesses all corroborated this teaching away by the art at the time the invention was made. Dr. Stites also wrote that monoclonals were disadvantaged by being "too specific", thus having the potential to result in cross-reactions with other than the antigen to which the assay is targeted. D. Stites, *supra.* This can lead to "false positive" results being given to

doctors who must rely on assays such as these to make medical decisions and prescribe treatment. Petitioner also omitted from its statement, arguing the supposed universal application of monoclonals, the fact that the record shows that people who tried to use monoclonals in performing the popular RIA got results that were not as good as those with prior art polyclonal RIAs (RA4-5).

In describing the prior art, Petitioner states that prior art sandwich assays form the three-part complex diagramed at page 4, "as the Federal Circuit stated in its opinion." What the court noted, however, was that Petitioner's figure is merely "illustrative of the sandwich complex" (PA4). This takes into account that polyclonal sandwich assays were not made by selecting at least first and second antibodies (as required by the patent) to bind to remote antigenic sites, which resulted in bound and labeled polyclonal antibodies competing with each other for the same epitopes. It is Respondent's invention that can be a true "two-site" or "selected-site" assay. This allows, for example, one to utilize under any conditions the beneficial assay format where all reactants can be added simultaneously to achieve the performance benefits noted above, including speed.

Petitioner's expert Blakemore admitted that a polyclonal sandwich assay she developed for the thyroid antigen TSH (which could be run in simultaneous format under certain specific conditions only, and was one of the three sandwich assays marketed in 1979) did not involve selection of antibodies that did not compete against each other for binding to the same epitopes (RA6). Further, Blakemore admitted that she had problems with her assay, including the need to run it sequentially rather than simultaneously when greater sensitivity was desired. Yet, even though she had been

aware of monoclonal antibodies for a number of years by that time, she never thought to solve those problems by changing her assay format to correspond to Respondent's invention (RA7). Indeed, expert Blakemore filed for a patent in December 1978 for her polyclonal sandwich assay, which was directed to all antigens, and *neither that application nor her patent*, which could have been amended at any time before its issuance in 1981, *even mentioned monoclonal antibodies* (PA27 n.5).

The trial of this action consumed 14 courtroom days during which time over thirty witnesses testified and eight others testified by deposition. The transcript is over 2000 pages in length. While there were almost 350 exhibits made of record, it was not until the final day of trial that over 100 of those exhibits, about which there had been not a word of testimony, were introduced into evidence. Final argument, limited to one hour per side was held the day following trial. Trial "summaries", limited to twelve pages and only facts (no citation of legal authorities was permitted), were filed on the day following trial. By noon on the third working day after final argument the trial court had issued its findings of fact and conclusions of law.

Those findings and conclusions were adopted almost entirely from Petitioner's pretrial brief and its pretrial proposed findings of fact and conclusions of law, none of which, of course, are referenced by citation to the record (PA6). The District Court, in adopting MAB's pretrial defenses, held Respondent's patent invalid on a variety of grounds under 35 U.S.C. §§102, 103, and 112. A full one half of the alleged prior art references relied upon by the trial court through its adopted findings were never discussed at trial. They were introduced into evidence almost as an afterthought at the close of trial,

together with almost 60 other articles cited by Petitioner that had not been the subject of any testimony or briefing.

The Court of Appeals analyzed the prior art and the evidence relied upon by the trial court. The Federal Circuit also analyzed the District Court's findings and conclusions, noting that Petitioner's pretrial brief and pretrial proposed findings and conclusions had been adopted "virtually verbatim". While expressing misgivings whether such findings satisfied the objectives of Rule 52(a), the court cited *Anderson v. City of Bessemer City, N.C.*, 470 U.S. 564 (1985), and observed that the trial court's findings were nevertheless its own and could be reversed only if clearly erroneous (PA13). Applying the clearly erroneous standard, the Court of Appeals reversed the lower decision, overturning particular findings and holding various legal conclusions to be erroneous as a matter of law, including the District Court's adoption of a number of Petitioner's pretrial claims of patent invalidity under 35 U.S.C. §112 for which *no evidence* had been introduced at trial.

SUMMARY OF ARGUMENT

The Court of Appeals for the Federal Circuit prepared a well reasoned opinion which carefully considered the evidence and the law. In particular, the opinion gave detailed and express consideration to the requirements of Rule 52(a).

Petitioner apparently seeks review to have this Court investigate whether the appellate court really did what it said it was doing. Because the Court of Appeals affirmatively followed this Court's directions regarding Rule 52, Petitioner is forced to say that despite the indicated adherence to that Rule, the Federal Circuit only paid "lip service" to it and thus asks this Court to duplicate a painstaking review of the evidence to

determine that the Court of Appeals was wrong when it held findings of the District Court clearly erroneous. None of the matters set out in this Court's Rule 17 can serve as the basis for such a review and Petitioner has not described any other ground on which this Court should accept certiorari.

We have shown *infra* that Petitioner has misstated the record and omitted critical facts in attempting to support its position. However, it is not necessary to look deeply into Petitioner's arguments about the record because it is clear from the opinion itself that the Federal Circuit made a detailed and appropriate consideration of the evidence and arguments and properly reached a definite and firm conviction that mistake had been committed in light of the record as a whole.

Contrary to the suggestion that the Federal Circuit systematically fails to follow Rule 52, a review of Federal Circuit cases indicates an awareness and sensitivity to that rule. The critical attack on Judge Rich, based upon remarks made to members of the bar, is inappropriate no matter what the remarks may have been. The attack is particularly inappropriate, however, because it is based upon Petitioner's misrepresentation of what Judge Rich really said, which was that Rule 52 is carefully adhered to in the Federal Circuit.

Petitioner's suggestion and request for summary determination by this Court that the invention is a mere substitution and thus *per se* obvious ignores both the law and the long list of facts demonstrating nonobviousness. Those facts establish that the present invention is much more than a substitution of monoclonal antibodies for polyclonal antiserum in a certain immunoassay protocol. First and second monoclonal antibodies having particular characteristics, according

to the invention, can be used in a specific way to achieve improved results not previously obtainable in any of the many types of immunoassays known. This Court has made clear that the law requires the invention as a whole be considered in resolving issues under 35 U.S.C. §103. The law is also clear that the obvious/nonobvious inquiry is not to be, and cannot be, resolved by a slogan relating to the manner in which the invention was allegedly made, e.g., substitution of materials.

The factual inquiries mandated by *Graham v. John Deere Co.*, 383 U.S. 1 (1966), and the requirement that the invention as a whole be examined reveal the "obvious to try" standard advocated by Petitioner to be equally in conflict with the law. Such an approach would mean that no matter how nonobvious the resulting invention, it would not be patentable if the manner in which the invention was made were logical. This ignores the realities of scientific research and shuns the statutory command that the entire invention be considered, including unexpected properties and results and the so-called "secondary considerations". It also ignores the Congressional mandate of 35 U.S.C. §103 that patentability shall not be negatived by the manner of making the invention.

No remand is required on diligence. The diligence determination by the Federal Circuit was based upon evidence never contested by Petitioner and was primarily based upon documentary exhibits. Furthermore, the determination of diligence was an alternative decision of the Federal Circuit and, thus, it would be an unnecessary exercise to remand for such a holding by the District Court.

This patent dispute is no different from many cases in other circuits where a Court of Appeals has reversed

based upon a determination that District Court findings were clearly erroneous, a not uncommon event over the years. Petitioner merely wishes this Court to summarily adjudge that the Federal Circuit was wrong in ruling against it and, on that basis, to issue the Writ sought.

ARGUMENT

I.

THE FEDERAL CIRCUIT DID NOT FAIL TO FOLLOW RULE 52

A. The Federal Circuit Specifically Referred to and Utilized Rule 52 in its Decision in this Case

We are content to rely upon the opinion of the Federal Circuit as our best advocate in refuting Petitioner's contention that the court did not properly apply Rule 52(a). The principles which guided the Federal Circuit in its analysis of the District Court's findings are clearly set forth at PA12-13. The Federal Circuit repeatedly relied upon the clearly erroneous standard in analyzing the findings of the District Court (PA15, 18-19, 21, 22, 26 and 31). It is equally manifest that the Federal Circuit carefully considered the record as a whole in concluding that the findings of fact of the District Court were clearly erroneous.

Petitioner recites certain facts which it contends support the findings of the District Court. We will demonstrate that, as the Federal Circuit determined, Petitioner is incorrect in that assertion. However, even if there is some evidence to support the findings, Petitioner's apparent contention that an appellate court must, under Rule 52, sustain the finding of a District Court if there is *any* evidence to support it is erroneous as a matter of law. As this Court said in *United States v. United States Gypsum Co.*, 333 U.S. 364, 395 (1948), *rehearing denied*, 333 U.S. 869 (1948):

> ". . . a finding is clearly erroneous when *although there is evidence to support* it, the reviewing court on the entire evidence is left with a definite and firm conviction that a

mistake has been committed." [Emphasis added.]

B. Judge Rich Has Consistently Exhibited Concern For Rule 52

In support of its claim that the Federal Circuit showed "total disregard" for Rule 52(a) and practiced a fraud in purporting to apply that standard, Petitioner has cropped a public speech, entitled "Thirty Years of This Judging Business," which was given by the author of the opinion. While regrettable in the extreme, it is also reflective of the merits of Petitioner's arguments for review that they are believed best supported by a personal attack on the authoring judge below, implying that he is lacking in either skill or legal competence or honesty. Notwithstanding the fact that the decision complained of was unanimous, that the opinion was joined in by two former Judges of the U.S. Court of Claims, and that such tactics cannot substitute for reasoned analysis, it is substantively undeniable that the speech quoted from by Petitioner cannot indict any of the Federal Circuit, the three-member panel below, or the authoring judge individually.

The speech itself represents a clear message to the bar that the Federal Circuit adheres strictly to its appellate role in reviewing findings of fact. Petitioner has craftily cropped the presentation quoted from, substituting a first ellipses for Judge Rich's statement that his court's emphasis is squarely on Rule 52(a) and "particularly the sentence" which sets out the confines of "clearly erroneous" and "credibility of witnesses". Petitioner also eliminated the very next statement that, therefore, "If a fact finding rests on conflicting testimony and the trial judge made a credibility determination, *you have very little chance of changing it*" (Emphasis

added). Also trimmed from Petitioner's quote — to impart a false understanding of the last-quoted sentence in its footnote 7, "Judge your chances on appeal accordingly." — is the warning by Judge Rich which immediately trails it: "To put it another way, win your case in the trial court."

In constructing its argument for this Court, Petitioner also kept to itself many opinions from the Federal Circuit written for it by Judge Rich where the court acknowledged and explained its limited appellate function, and where it rigorously applied Rule 52(a) and the associated principles that have been announced by this Court. The Court's attention is directed to, for example: *Preemption Devices, Inc. v. Minnesota Mining and Mfg. Co.*, 732 F.2d 903, 905 (Fed. Cir. 1984); *State Industries, Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1232 (Fed. Cir. 1985); *Studiengesellschaft Kohle, M.B.H. v. Dart Industries, Inc.*, 726 F.2d 724, 727 (Fed. Cir. 1984); *Gardner v. TEC Systems, Inc.*, 725 F.2d 1338, 1344-45 (Fed. Cir.) (in banc), *cert. denied*, 469 U.S. 830 (1984).[2]

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[2]In response to Petitioner's claim that the Federal Circuit as a court has schemed to ignore Rule 52, we note that the Federal Circuit has consistently exhibited an appreciation and an understanding of this Court's directions regarding the application of Rule 52, as well as a concern that Rule 52 be properly applied. Apparently to show the contrary, Petitioner places reliance on *Dennison Mfg. Co. v. Panduit Corp.*, 106 S.Ct. 1578 (1986), where this Court remanded a decision of the Federal Circuit because it had not mentioned Rule 52(a) in overturning District Court findings. *Panduit* is not relevant to Petitioner's cause. The Federal Circuit here thoroughly discussed Rule 52 and expressly applied its clearly erroneous standard, as the court has done on many previous occasions.

Even an abbreviated listing of Federal Circuit cases involving Rule 52(a) indicates that the court has consistently adhered to the

C. The Federal Circuit's Observation on the Credibility of Ruoslahti's Claim of Actual Reduction to Practice in November 1979 Does Not Violate Rule 52

At page 17 of the Petition, the Federal Circuit's observation on the credibility of Ruoslahti's claim of prior invention in November 1979 is erroneously criticized as a reversible violation of Rule 52. The Federal Circuit did not make a detemination of Ruoslahti's credibility, but merely referred to a certain document as "bearing on the credibility of Ruoslahti's testimony" — a document which ruled that LJCRF had in a Patent Office proceeding previously been unable to prove prior invention at *any time* before Respondent's August 1980 filing date, let alone in November 1979. Other evidence directly refuting Petitioner's claim of prior invention by Ruoslahti included his own written list of the earliest

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clearly erroneous standard since its formation in 1982: *Revlon, Inc. v. Carson Products Co.*, 803 F.2d 676, 678 (Fed. Cir. 1986), *cert. denied*, 107 S.Ct. 671 (1986); *Windsurfing International, Inc. v. AMF Inc.*, 782 F.2d 995, 1000 (Fed. Cir.), *cert. denied*, 106 S.Ct. 3275 (1986); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 313 (Fed. Cir. 1985); *In re Mark Industries*, 751 F.2d 1219, 1222-23 (Fed. Cir. 1984); *Litton Systems, Inc. v. Sundstrand Corp.*, 750 F.2d 952, 956 (Fed. Cir. 1984); *Stock Pot Restaurant, Inc. v. Stockpot, Inc.*, 737 F.2d 1576, 1578-79 (Fed. Cir. 1984); *Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1573 (Fed. Cir. 1984); *Vandenberg v. Dairy Equipment Co.*, 740 F.2d 1560, 1565 (Fed. Cir. 1984); *Seattle Box Co. v. Industrial Crating & Packing, Inc.*, 731 F.2d 818, 823 (Fed. Cir. 1984); *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1535 (Fed. Cir. 1983); *Carl Schenck, A.G. v. Nortron*, 713 F.2d 782, 785 (Fed. Cir. 1983).

Petitioner's allegation at page 11, that the Federal Circuit has shown a continuing disregard for Rule 52 is thus completely at odds with the repeated indications of adherence to that Rule by the Federal Circuit.

dates LJCRF could assert for his alleged work (which dates were all in 1980, much later than the 1979 date he testified to). The Federal Circuit also point out that: (1) there were unexplained alterations of the only notebook page Ruoslahti relied upon in his testimony, which showed only several graphs, and noted that in addition to the alterations, the page was not signed, witnessed or dated; (2) the notebook author and alleged co-inventor Uotila could not remember the procedure allegedly run to obtain the data graphed on the page and testifed that there was not enough information in the notebook to refresh her memory; (3) neither Ruoslahti nor Uotila could find any data in the notebook supporting the notebook page; (4) a third alleged co-inventor testifed that there was nothing about the shape of the curves which indicates they reflect sandwich assays; (5) none of the later graphs in the notebook represented a successful assay; and, (6) that severe problems were encountered after the work on the disputed page was concluded (PA20-21). Thus, the record as a whole provides ample basis for serious concern about the credibility of Ruoslahti's *statement* that he reduced the invention to practice in November 1979. Petitioner does not make a contrary contention.

The Federal Circuit did not discount the testimony of Ruoslahti in favor of another witnesses' testimony but rather tested Ruoslahti's conclusory statement with inconsistencies in his own testimony, with the testimony of his co-workers, and with the documentary evidence. The Federal Circuit did not hold that findings regarding the alleged LJCRF work were clearly erroneous, but rather that the facts were "legally inadequate" to establish a conception or reduction to practice (PA20). It was clearly proper for the Court of Appeals to evaluate Ruoslahti's claim in light of documentary evidence and

internal inconsistencies. In *United States v. United States Gypsum Co.*, 333 U.S. 364, 396 (1948), *rehearing denied*, 333 U.S. 869 (1948), this Court gave little weight to that kind of testimony, stating:

> Where such testimony is in conflict with contemporaneous documents we can give it little weight, particularly when the crucial issues involve mixed questions of law and fact. Despite the opportunity of the trial court to appraise the credibility of the witnesses, we cannot under the circumstances of this case rule otherwise than that Finding 118 is clearly erroneous.

Petitioner points out that the trial court listed a group of witnesses, which was comprised of every one of Petitioner's witnesses save several of its employees, to be "credible." But the trial court cannot insulate its findings from review by such a recitation, which did not include a determination that any finding was based on a credibility decision. This Court in *Anderson v. Bessemer City*, 470 U.S. 564, 84 L.Ed.2d 578, 529 (1985), stated that a Court of Appeals may well overturn a finding that was said to be based on a credibility evaluation, noting that a trial judge may not

> insulate his findings from review by denominating them credibility determinations, for factors other than demeanor and inflection go into the decision whether or not to believe a witness. Documents or objective evidence may contradict the witness' story; or the story itself may be so internally inconsistent or implausible on its face that a reasonable fact finder would not credit it. Where such factors are present, the Court of Appeals may well find clear error

> even in a finding purportedly based on a credibility determination. See, e.g., *United States v. United States Gypsum Co., supra,* at 396, 92 L Ed 746, 68 S Ct 525.

Thus, in light of the record as a whole, we suggest that the so-called "smoking gun" is not in the Federal Circuit's hand but rather in Petitioner's hand in the form of Ruoslahti's unsupportable claim, as properly determined by the Federal Circuit.

D. The Federal Circuit Properly Applied Rule 52 in Reviewing Evidence of Conception

At pages 11-15, Petitioner embarks on a detailed fact argument intended to show that the Federal Circuit was simply wrong in its application of Rule 52(a) to the question of conception of the invention by Hybritech. This analysis fails to address itself to any issue for which the granting of a writ might be appropriate under Rule 17 of this Court and, again, we rely on the Federal Circuit's opinion as the best evidence in refutation (PA 16-19). However, to the extent this factual argument may be construed as a contention that the Federal Circuit is engaged in a conspiracy to acknowledge Rule 52(a) and yet routinely ignore its requirements (Petition at 8 and 11), we briefly respond by showing that Petitioner's claims are not supported by the record.

Petitioner is wrong in contending that a January 1979 conception date is "critical" to Respondent's case. Assuming no prior reduction to practice, establishment of a date of conception by Respondent prior to its August 1980 patent application filing date would have been "critical" only (1) if the alleged LJCRF work had been found to be a reduction to practice of the invention, or even a conception, prior to August 1980 or (2) if

the December 1979 Herzenberg article had been found to be an invalidating description of the invention. Neither were and, therefore, the establishment of a conception date is alternative to the Federal Circuit's decision against Petitioner. Further, even if the alleged LJCRF work or the Herzenberg article had been held to otherwise invalidate the patent, a reduction to practice by Respondent before November 1979 predated such activities, as Petitioner admitted at trial (but omitted here) (PA17-18). This earlier reduction to practice eliminates both as prior art.

The Federal Circuit reversed as clearly erroneous the trial court's finding that there was no credible evidence of conception prior to May 1980, remarking that there plainly was and holding that such evidence, including laboratory notebooks from August, September and October 1980 — as well as the admission of Petitioner's own patent law expert that Respondent invented first, was legally sufficient to establish a conception of the claimed invention (PA16-18). Petitioner has made no contention that this evidence does not establish a conception and reduction to practice of the invention.

Petitioner implies that there is a finding that Dr. David was not credible. There was no such finding but rather only a statement that various other witnesses were credible. The failure to make a finding regarding that credibility of Dr. David is not a determination that he is not credible.

Petitioner's contention that the Federal Circuit conceded that conception was "sparsely documented" misses the mark. A conception may be evidenced by a single document and the Court of Appeals merely stated that conception was "evidenced by the sometimes sparsely documented work of a start-up company . . ."

However, documentation evidencing conception and reduction to practice in the Summer and Fall of 1979, long before the alleged LJCRF work, was not "sparse," but rather included notebook pages and memoranda which provides enough documentation for Petitioner's patent law expert to admit Respondent's prior invention through an August 1979 reduction to practice using monoclonal antibodies (designated "068") having the claimed affinity (PA18).

Thus, it is clear that there was ample documentary and testimonial evidence to support the Federal Circuit's legal conclusion that the date of conception was at least before November 1979, thus predating the alleged LJCRF work and the Herzenberg article (PA16). As is plain from the Petition, there is no argument with this legal conclusion.

E. The Federal Circuit Properly Applied Rule 52 in Holding that the District Court's Finding on Commercial Success Was Clearly Erroneous

Petitioner contends that the Federal Circuit did not properly analyze the facts regarding commercial success solely because it did not take into account the "lead time" necessary to develop an assay. This is alleged to be "a reason" for the commercial success that Petitioner admits, although Petitioner does not reveal its weight.

Lead time is a new theory not advanced below. The trial court made no findings regarding lead time. In any event, Petitioner is wrong in contending that the time to develop a particular assay is three years. Both Respondent and Petitioner made their first assays, received FDA approval after testing, and put them on the market in less than two years. Petitioner's time to market was less than Respondent's, it having had the benefit of copying the invention from Respondent.

However, even assuming that three years were the time required to develop an assay (and that one should mark the beginning of that time period at the "founding" of the Respondent company in October 1978, as suggested at page 18), the point which Petitioner ignores is that everyone should have been on the market in 1981 because Petitioner acknowledged that monoclonal antibodies were widely available at least in 1978 (PA26). The facts are that nobody was on the market when Respondent introduced its monoclonal assays in June 1981 and even with Respondent's success, only Petitioner had entered the market by the end of 1982. Additionally, of course, "lead time" does not explain the commercial success that Petitioner has reaped by its infringement of the patent-in-suit.

II.

THE TRIAL COURT USED ALMOST VERBATIM AS ITS OPINION PETITIONER'S PRETRIAL BRIEF AND PRETRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

As noted, the District Court saw fit to rule in favor of Petitioner by a virtual adoption of Petitioner's *pre-trial* brief and *pre-trial* proposed findings of fact and conclusions of law as its opinion. While the District Court eliminated all references to Petitioner's lone noninfringement defense and to its validity defense of fraud in the Patent Office, Respondent was never asked, nor given an opportunity, to respond to those pre-trial papers. Accordingly, the opinion of the District Court reflected more the pre-trial views of a lawyer than it did the record in this case. Indeed, as the Court of Appeals noted, this adoption of pre-trial submissions resulted in "facts" being found and "issues" being decided

that were *not the subject of evidence at trial* (PA13). Petitioner admitted as much by abandoning on appeal one of its two anticipation defenses under 35 U.S.C. §102 and half of its six 35 U.S.C. §112 defenses, even though the District Court had ruled in its favor on each of them by adopting its pretrial allegations.[3]

Petitioner incorrectly states that there was "no reason" for the Federal Circuit to remark that the District Court used nearly verbatim Petitioner's pre-trial arguments in producing its opinion "other than to disparage" the lower court. This Court, as well as every circuit that has addressed the issue, has condemned the practice of even having the prevailing party *after decision* prepare the lower court's findings and conclusions. Such a practice has been particularly criticized "when those findings have taken the form of conclusory statements unsupported by citation to the record." *Anderson v. City of Bessemer City*, 84 L.Ed 2d 518, 527 (1985). The fact that there are no citations to the record in the lower court's opinion here, aside from exhibit numbers identifying several publications, is because Petitioner's adopted *pre-trial* papers could not have contained such citations.

Notwithstanding the District Court's method of announcing its decision the Federal Circuit did not base its judgment upon the District Court having engaged in this disapproved practice. The Court of Appeals emphasized that "those findings are the District Court's and may be reversed only if clearly erroneous", citing

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[3]It is equally noteworthy that Petitioner has abandoned here its remaining Section 112 invalidity claims, which were characterized by the Federal Circuit as "utterly baseless" (PA29), thus leaving in the case only a single claim under each of sections 102 and 103 from Petitioner's original eleven defenses. Petitioner's 35 U.S.C. §102 defense is based on its claims regarding LJCRF.

Anderson (PA13). Petitioner's reference to a speech by Federal Circuit Chief Judge Markey, where he espoused the benefits of deciding a case from the bench, is not pertinent. Even a cursory reading of Judge Markey's article indicates that, although he advocated a decision shortly after trial, he also emphasized that the trial court "will do what's appropriate in due course in the way of findings and conclusions." Preparing findings by adopting pretrial briefs and proposed pretrial findings is hardly "appropriate".

The fact that the Federal Circuit noted the District Court's reliance on the universally discouraged practice of adopting findings and conclusions without record citation and without comment from the other side, therefore, does not support Petitioner's case for review. Further, the suggestion at page 19, that Judge Conti recused himself because of the Federal Circuit's proper comments is baseless and inappropriate. No reason was given for his recusal, although new conditions existed at the time of recusal including new parties in interest. Thus, Petitioner's attempt to rely on Judge Conti's recusal as a dissent should be ignored.

III.

THE FEDERAL CIRCUIT PROPERLY APPLIED THE LAW ON OBVIOUSNESS

A. Petitioner's Argument on "Substitution" Is A Strawman Stuffed With Misrepresentation and Knocked Down With Inapt Precedent

Contrary to Petitioner's lead off misstatement, there is no finding that the only difference between the claimed invention and the prior art was the substitution of monoclonal antibodies for polyclonal antisera. As explained *supra*, for example, the claimed invention has

been a tremendous commercial success due to its unexpectedly superior and medically significant attributes, and today a majority of the assays introduced into the market are sandwich-type assays using certain monoclonal antibodies. Even Petitioner hails the great differences in the claimed invention, emphasizing in its Annual Reports and promotional literature that it is *faster, simpler, more accurate,* and *more sensitive* that what went before. In fact, Petitioner recently described the patented process it infringes as a "pioneering approach", and earlier stated that "Over the next five years, older, conventional methods of testing are expected to shrink in use and some may disappear completely". Monoclonal Antibodies, Inc., 1984 Annual Report, Plaintiff's Trial Exhibit 1. Thus, contrary to Petitioner's "mere substitution" argument, it is plain — and it is admitted — that the "invention as a whole" is much, much more.

This Court emphasized in *United States v. Adams,* 383 U.S. 39, 50-51 (1966), there can be no "mere substitution" in fact where the characteristics of the claimed invention are different from those found in the prior art:

> Nor is the government's contention that the electrodes of Adams were mere substitutions of pre-existing battery designs supported by the prior art. If the use of magnesium for zinc and cuprous chloride for silver chloride were merely equivalent substitutions, it would follow that the resulting device — Adams' — would have equivalent operating characteristics. But it does not.

This Court in *Adams* also relied on the disbelief of experts in support of its conclusion of patentability. Similarly, there is the uncontradicted trial testimony here of experts in the fields of pregnancy testing, human

growth deficiency testing, and thyroid testing that they were surprised that the claimed invention worked and, indeed, that it worked so much better than the best prior art assays (PA27-28). Even Petitioner's own expert stated of the invention: "I don't personally know of anything better. . . ." (RA8).

It is equally clear, however, that the trial court ignored the above evidence and distinguishing aspects of the invention in adopting most of Petitioner's pretrial brief as its opinion. That refusal led the Federal Circuit, properly, to admonish that the trial court had failed to consider the invention as a whole, as it was required by law to do.

Petitioner at pages 22-23 attempts to construe the language of the Federal Circuit as error. But the Court of Appeals' language is merely indicative of its effort to be faithful to the law, which requires that it is the invention "as a whole" which must be tested for obviousness. Thus, the Federal Circuit criticized the trial court for focusing only on the obviousness of claim language differences, that focus being contrary both to 35 U.S.C. §103 and the direction of this Court. *E.g., Parker v. Flook*, 437 U.S. 584, 594 n.16 (1978).

Each obviousness determination must be judged on its own facts. Petitioner's citation of *Hotchkiss v. Greenwood* and suggestion that monoclonal antibodies isolated from immortal hybridoma fusion cell cultures involve the same considerations as clay doorknobs, and that sandwich immunoassays are similar to clay knobs with metallic shanks, stretches a bad analogy far beyond its breaking point. In essence, the suggestion that the same result should necessarily apply in both cases is a specific rejection of the statute and the factual inquiries dicated by *Graham v. John Deere Co.*

B. Petitioner's Suggested Obvious To Try Test for Patentability Is Equally at Odds with the Law

At page 25, Petitioner relies upon its overturned pretrial claims of "suggestions to use" monoclonals for everything and argues that the trial court's obvious to try approach is the proper test for obviousness. But such an approach is at odds with 35 U.S.C. §103, over 20 years of case law from the circuits, and the instruction of this Court.

The Court of Customs and Patent Appeals long ago rejected the attempt to substitute an "obvious to try" inquiry as the standard or test of patentability under 35 U.S.C. §103. *In re Huellmantel,* 324 F.2d 998, 1001 n.3 (CCPA 1963). According to the court, speaking through Judge Rich, co-author of the 1952 Patent Act where section 103 finds its origin, that approach merely

> begs the question, which is obviousness under §103 of *compositions* and *methods*, not of the direction to be taken in making *efforts* or *attempts*. Slight reflection suggests, we think, that there is usually an element of "obviousness to try" in any research endeavor, that it is not undertaken with complete blindness but rather with some semblance of a chance of success, and that patentability determinations based on that as the test would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of "research." [Emphasis by the court.]

In re Tomlinson, 363 F.2d 928, 931 (CCPA 1966). Serendipity is not a prerequisite to patentability. *In re Lindell,* 385 F.2d 453, 455 (CCPA 1967). Additionally,

of course, acceptance of "obvious to try" as the standard of 35 U.S.C. §103 would be in complete disregard of the invention "as a whole" mandate of that statute. *In re Goodwin*, 576 F.2d 375, 377 (CCPA 1978); *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977).

Thus, Petitioner's obvious-to-try "standard" not only involves a long-since rejected analysis for which there is no authorization but it precludes a consideration of the invention as a whole for which there is an explicit statutory directive. *Roberts v. Sears, Roebuck & Co.*, 723 F.2d 1324, 1334 (7th Cir. 1983) (en banc); *Novo Industri A/S v. Travenol Laboratories, Inc.*, 677 F.2d 1202, 1208 (7th Cir. 1982); *Trio Process Corp. v. L. Goldstein's Sons, Inc.* 461 F.2d 66, 72 n.18a (3rd Cir. 1972), *cert. denied*, 409 U.S. 997 (1972). Of course, the case law also belies Petitioner's conclusion that "obvious to try" is merely "a meaningless slogan-type standard", which it apparently suggests is employed by the Federal Circuit "simply to justify a reversal of the trial court." Petitioner further errs in its claim that the Federal Circuit assumes that "evidence it choses to label as 'obvious to try' evidence is automatically of no weight." The Federal Circuit did not "automatically" exclude the evidence, but rather analyzed the references in question and the record to conclude that they "do not suggest how that end might be accomplished " (PA23).

IV.

REMAND IS NEITHER NECESSARY NOR APPROPRIATE

Petitioner's request for a remand is truly an afterthought, unsupported by substance. Although Respondent urged reversal and emphasized in its opening brief on appeal that no remand was necessary, Petitioner did not suggest the appropriateness of a remand in any of its arguments to the Federal Circuit until after the court had reversed. Even then, Petitioner did not contest diligence or make the argument which it now asserts, that a remand was necessary for a ruling on diligence. That theory is presented for the first time in this Court.

There are many reasons, however, why a remand is not necessary or appropriate. First, there was neither evidence nor argument contradicting the Federal Circuit's determination of diligence and, thus, it was an inescapable conclusion. Second, the determination of diligence was made primarily from a documentary record. Finally, and perhaps most important, the court's conclusion on diligence was alternative to its holding, both because the evidence of alleged LJCRF work was inadequate as a matter of law to show the claimed invention and the court considered the most pertinent references, and because Petitioner's expert admitted at trial that Respondent reduced its invention to practice long before both the claimed LJCRF activities relied on by Petitioner and the several, merely cumulative articles which Petitioner erroneously says now, for the first time, are "the most relevant".

Respondent's proofs included laboratory notebook pages and other documentary exhibits showing diligent attention to the development of the invention through 1979 and the first half of 1980. On the basis of these

documents alone, it was possible for the Court of Appeals to make a determination on the diligence which Petitioner never contested. The documents were primarily introduced through Dr. David who testified for approximately a day and a half explaining and describing the large volume of documents witnessing diligence. As noted by the Federal Circuit (PA19), there was

> absolutely no evidence of record nor even argument by Monoclonal that Hybritech was not diligent in its efforts to reduce to practice the claimed invention during the period January 1979 to the application filing date of August 4, 1980.

Nevertheless, Petitioner now argues that there should have been a remand to the District Court to rule on diligence. There is no need for a remand when the record permits only one resolution of the issue. *Dayton Board of Education v. Brinkman*, 443 U.S. 526, 534-537 (1979), *rehearing denied,* 444 U.S. 887 (1979); *Bigelow v. Virginia*, 421 U.S. 809, 826-27 (1975); *Levin v. Mississippi River Fuel Corp.*, 386 U.S. 162, 170 (1967) ("Effective judicial administration requires that we dispose of the matter here"). Where, as here, the evidence of diligence is primarily documentary, there is even less necessity of review by the District Court. *United States v. General Motors Corp.*, 384 U.S. 127, 141-42 n.16 (1966); *Jennings v. General Medical Corp.*, 604 F.2d 1300, 1305 (10th Cir. 1979).

Petitioner's reliance on *Icicle Seafoods, Inc. v. Worthington*, 106 S.Ct. 1527 (1986) is misplaced because in *Icicle* the Court of Appeals neither discussed nor analyzed the contrary findings of the District Court, but reviewed the record independently and found facts

inconsistent with the District Court's findings. Here, unlike *Icicle*, the District Court made no diligence determination, and the diligence evidence was undisputed. Of course, remand is also needless because diligence was discussed in connection with the alleged prior work by LJCRF and with respect to several irrelevant, non-prior art references, one of which was *written by Respondent in 1980*. The first date alleged for carrying out the invention by LJCRF was in early November 1979 (PA20). However, in addition to the testimony of Petitioner's own expert that Respondent made the invention first, in August 1979, (thus eliminating several cumulative articles of the more than 80 cited by Petitioner, the fully considered Oi/Herzenberg and Frankel works so heavily relied on and emphasized by Petitioner being "the most pertinent" (PA24)), the Federal Circuit held that the work relied upon to establish a reduction to practice by LJCRF was "legally inadequate to support even a holding of conception of the claimed invention by LJCRF personnel in 1979" (PA20). Therefore, the facts relied upon by Petitioner and the District Court to establish conception and reduction to practice by LJCRF were legally inadequate for that purpose and the holding of the Federal Circuit that there was diligence from a time prior to that alleged work is an alternative one.

Petitioner suggests that remanding on the issue of patent infringement but not on the issue of diligence is troubling. The two issues are readily distinguishable. Infringement is an entire issue on which the trial court entered no express findings. An infringement determination decides whether there is liability. On the other hand, the issue of diligence relates to validity and is merely one factor to be considered on the issue of priority of invention, and only if necessary. In this case, in view

of Petitioner's admission and the inadequacy of its LJCRF proofs, a diligence determination is not required in order to hold that the activities of LJCRF and several publications were not prior art. Accordingly, there is a great difference between the collateral issue of diligence and the determination of infringement.

CONCLUSION

For the reasons above, the Petition for Writ of Certiorari to the Federal Circuit should be denied on all issues. The Petition should also be denied under this Court's Rule 21.5 because Petitioner failed to adequately present those facts "essential to a ready and adequate understanding" of its arguments, forcing Respondent to provide them instead and to correct Petitioner's misreporting of the record.

Respectfully submitted,

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APPENDIX

SOLUBLE PROTEIN MEASUREMENT

A. Precipitation
- Radialimmunodiffusion
- Immunoelectrophoresis
- Electroimmunodiffusion
- Nephelometry
- Ring Test
- Oudin Tube

B. Agglutination
- Latex
- Hemagglutination
- Particle Enhanced Nephelometry

C. Radioisotopic
- RIA
  - Double Antibody
  - Solid Phase
- IRMA
  - Non Sandwich
  - Sandwich
- Radioimmunoelectrophoresis

D. Enzymatic
- Enzyme Immunoassay
- IEMA
- EMIT

E. Fluorometric
- FIA - Fluoroimmunoassay
  - Enzyme Mediated
  - Direct FIA
- IFMA - Immunofluorometric
  - Enzyme Mediated
  - DIrect IFMA
- Fluoresence Quenching Enhancement
- Fluoresence Polarization
- Time Phase Fluoresence

F. Electron Spin Resonance

G. Chemilluminesence

Q. YOU KNOW THAT BY 1979 A LARGE NUMBER OF COMMERCIAL COMPANIES WERE MAKING MONOCLONAL ANTIBODIES; ISN'T THAT CORRECT?

A. BY '79? WHAT PART? BEGINNING OF '79, LET'S SAY?

Q. SURE.

A. BEGINNING OF 79—I DON'T THINK THERE WERE A LARGE NUMBER AT THAT POINT. I'M NOT SURE. I DON'T KNOW HOW MANY WERE MAKING THEM. ABOVE I DOUBT ANYWHERES NEAR THE NUMBER THAT ARE NOW DOING IT.

Q. CERTAINLY THERE WERE A VERY LARGE NUMBER OF DIFFERENT LABORATORIES USING MONOCLONAL ANTIBODIES AT THE BEGINNING OF 1979; ISN'T THAT CORRECT?

A. I WOULD SAY THAT THERE WERE PROBABLY ONE HUNDRED OR MORE LABORATORIES, IF THAT'S A LARGE NUMBER, MORE THAN ONE HUNDRED.

Q. WOULDN'T YOU SAY THAT BY 1979 THE NUMBER OF PEOPLE WHO WERE MAKING MONOCLONAL ANTIBODIES WAS IN THE THOUSANDS?

A. MAYBE I SAID THAT IN MY DEPOSITION. BUT '79—BEGINNING OF '79—THE MEETING AT THE NIB WAS IN '78, I THINK WE DECIDED. IT GOT PUBLISHED IN '78. I THINK THE MEETING WAS HELD EARLY THAT YEAR IN THE SPRING.

AT THAT TIME THERE WERE WELL OVER ONE HUNDRED PEOPLE PRESENT, PERHAPS ALMOST 200. AND SO THE WORD PROBABLY SPREAD PRETTY RAPIDLY.

HERZENBERG-CROSS 11-1418

I CERTAINLY DON'T THINK I EVER COUNTED THEM. IT IS IN THE HUNDREDS OR THOUSANDS. I WOULD MORE LIKE TO AIM TOWARDS THE HUNDREDS ON REFLECTION. IT IS A LARGE NUMBER. . . .

Q. YOU HAVE USED MONOCLONAL ANTIBODIES IN SOME RIA COMPETITIVE ASSAYS?

A. IN SOME COMPETITIVE ASSAYS, CORRECT, BUT NOT NECESSARILY RADIOIMMUNOASSAY.

Q. HAVE YOU USED MONOCLONAL ANTIBODIES IN RADIOIMMUNOASSAYS?

A. HAVE I PERSONALLY USED A MONOCLONAL ANTIBODY IN A CONVENTIONAL RIA, IS THAT WHAT YOU ARE ASKING?

Q. YES.

A. I DON'T REALLY RECALL IF I HAVE OR NOT. IT WOULDN'T HAVE BEEN A ROUTINE ACTIVITY.

Q. IN THE COMPETITIVE ASSAYS THAT YOU HAVE PERFORMED, YOU HAVE HAD POLYCLONAL ANTIBODIES PERFORM BETTER THAN MONOCLONAL ANTIBODIES, ISN'T THAT CORRECT?

A. NOT THAT I PERSONALLY PERFORMED IN COMPETITIVE ASSAYS. I DON'T RECALL THAT I MADE THAT DIRECT COMPARISON.

Q. I'D LIKE TO READ FROM YOUR DEPOSITION—

A. WHICH PAGE?

Q. STARTING AT PAGE 80. LOOK AT LINE 17. I'D LIKE TO READ THERE.

> "Q. I AM TALKING ABOUT THE SAME, EXCEPT IN ONE CASE YOU USED MONOCLONAL ANTIBODIES, IN ANOTHER CASE YOU USED POLYCLONAL ANTIBODIES."

COLLOQUY. THEN LINE 24:

> "IN OUR ANTIBODY DEVELOPMENT, THEIR SCREENING PROCESSES DO COMPARE, AND IT USED TO BE THEIR IN-HOUSE CONTROL WAS A POLYCLONAL

AND OFTENTIMES OUR MONOCLONALS DID NOT PERFORM AS WELL.

Q. THAT'S IN THE SCREENING PROCESS BEFORE YOU PICKED THE RIGHT MONOCLONAL ANTIBODY PAIR; IS THAT RIGHT?

A. IT IS JUST IN THEIR CHARACTERIZATION OF ANTIBODIES, SOME OF WHICH ARE USED IN IMMUNOASSAYS. EVEN THOUGH NOT RADIOIMMUNOASSAY, THEY DID NOT PERFORM AS WELL AS THE CONTROL.

Q. AS TO SOME RADIOIMMUNOASSAYS YOU HAVE HAD POLYCLONAL ANTIBODIES PERFORM BETTER THAN MONOCLONAL ANTIBODIES; IS THAT RIGHT?

A. YES. AND THOSE ARE THE ONLY DIRECT COMPARISONS WHERE YOU JUST INSTITUTED THE TWO THAT I CAN RECALL."

IS THAT CORRECT?

A. THAT'S CORRECT. BUT I DID NOT PERFORM THOSE ASSAYS. ANOTHER DEPARTMENT DID. THAT IS WHAT YOUR QUESTION WAS.

Q. YOUR TSH ASSAY USED TWO ANTIBODIES BOTH DIRECTED—POLYCLONAL ANTIBODIES—BOTH OF WHICH WOULD BIND TO THE SAME EPITOPES, ISN'T THAT RIGHT?

A. TO THE BEST OF MY KNOWLEDGE, THAT IS TRUE.

Q. SO YOUR SANDWICH ASSAY DID NOT INVOLVE SELECTING ANTIBODIES THAT DON'T INTERFERE WITH EACH OTHER, DID IT?

A. THE ASSAY THAT WAS COMMERCIALIZED FOR TSH DID NOT INVOLVE SELECTING OF ANTIBODIES WHICH DID NOT INTERFERE WITH EACH OTHER.

A. THAT IS CORRECT.

Q. AND BY 1980, YOU WERE AWARE OF ADVANTAGES OF USING MONOCLONAL ANTIBODIES IN SANDWICH ASSAYS?

A. THAT IS CORRECT.

Q. AND BY 1980, YOU WERE AWARE OF PROBLEMS WITH YOUR SANDWICH ASSAY USING POLYCLONAL ANTIBODIES?

A. THAT IS CORRECT.

Q. AND YOU NEVER SUBSTITUTED OR SELECTED MONOCLONAL ANTIBODIES TO REPLACE POLYCLONAL ANTIBODIES IN YOUR TSH KIT, DID YOU?

A. NOT WHEN I WAS THERE, NO.

Q. BASED UPON THE POLYCLONAL ASSAYS THAT YOU ARE AWARE OF, IT WOULD BE A RETROGRESSION, WOULDN'T IT?

A. I DON'T KNOW PERSONALLY OF ANYTHING BETTER THAN WHAT IS OUT THERE ON THE MARKET.

Q. YOU ARE REFERRING TO THE MONOCLONAL SANDWICH ASSAY?

A. YES.

Q. AND THE MONOCLONAL ASSAY IS SOMETHING WHICH IS ADDED TO THE SUM OF HUMAN KNOWLEDGE, ISN'T THAT RIGHT?

A. ADDED TO THE SUM OF HUMAN KNOWLEDGE. YOU MEAN IN GENERAL?

Q. YES.

A. YES.

PROOF OF SERVICE BY MAIL

State of California

ss.

County of Los Angeles

I, the undersigned, say: I am and was at all times herein mentioned, a citizen of the United States and a resident of the County of Los Angeles, over the age of eighteen (18) years and not a party to the within action or proceeding; that my business address is 11333 Iowa Avenue, Los Angeles, California 90025; that on March 11, 1987, I served the within *Brief in Opposition to Petition for Writ of Certiorari* in said action or proceeding by depositing true copies thereof, enclosed in a sealed envelope with postage thereon fully prepaid, in the United States mail at Los Angeles, California, addressed as follows:

Clerk, United States
Supreme Court
One First Street, N.W.
Washington, D.C. 20543
(Original and forty copies)

David J. Brezner, Esq.
Flehr, Hohbach, Test,
Albritton & Herbert
Four Embarcadero Center
San Francisco, California 94111

I declare under penalty of perjury that the foregoing is true and correct. Executed on March 11, 1987, at Los Angeles, California.

Sharon L. Stewart
(Original signed)

(3)

No. 86-1318

In the Supreme Court

OF THE

United States

OCTOBER TERM, 1986

MONOCLONAL ANTIBODIES, INC.,
Petitioner,

VS.

HYBRITECH, INC.,
Respondent.

REPLY BRIEF FOR PETITIONER TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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ABBREVIATIONS

MAB	Monoclonal Antibodies, Inc.
Hybritech	Hybritech, Inc.
LJCRF	La Jolla Cancer Research Foundation
Opp.	Respondent Hybritech's Brief
"B"	Petitioner's Appendix to its Reply Brief
l/m	liters/mole

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INTRODUCTION

Hybritech's reliance upon the Federal Circuit's reference to the Rule 52(a) standards as evidence that those standards were in fact properly applied, is insufficient explanation of the specific examples of *de novo* review cited by MAB in its Petition. Misapplication of Rule 52(a), regardless of whether the proper standard was set forth, presents a truly unique situation where this Court's correction is needed.

Hybritech's arguments in support of the patentability of its claimed monoclonal sandwich assay inadequately respond to MAB's argument that the Federal Circuit, in applying the obviousness standard of patentability, has ignored this Court's precedents in *Hotchkiss* and *Graham*.

Furthermore, Hybritech has failed to justify the Federal Circuit's substitution of its own factual findings for those it found inadequate as well as its *de novo* finding on diligence. Diligence, an unusually stringent inquiry, is based substantially upon the *credibility* of the inventors. Such an inquiry should be decided, in the first instance, by the trial court, not the appellate court.

ARGUMENT

I

HYBRITECH IS CORRECT THAT MAB SEEKS REVIEW OF WHETHER THE FEDERAL CIRCUIT, IN FACT, FOLLOWED RULE 52(a)

MAB agrees with Hybritech that the Federal Circuit generally set forth the standards of review under Rule 52(a). Yet, the relevant inquiry is whether the Federal Circuit, albeit in good faith, *in practice* improperly applied those standards.[1] As conceded by Hybritech, the Federal Circuit opinion is the best evidence of whether the Court gave appropriate deference to the

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[1] Hybritech falsely asserts MAB argued that under Rule 52(a), if there is any evidence to support a finding of the trial court, an appellate court must sustain it. MAB correctly set forth the appropriate standards in its Petition, at p. 10.

trial court. It is apparent from the Federal Circuit's opinion that it misapplied Rule 52(a) by substituting its own findings on Hybritech's priority date, commercial success, and LJCRF's reduction to practice date for those of the trial court. (See Petition, pp. 11-18) Upon review of the decision it is apparent a *de novo* appellate review was conducted compelling Certiorari.

II

THE FEDERAL CIRCUIT DID NOT HOLD HYBRITECH HAD REDUCED THE CLAIMED INVENTION TO PRACTICE IN AUGUST, SEPTEMBER OR OCTOBER 1979

The Federal Circuit, reversing the trial court's findings, held Hybritech conceived the claimed invention by January, 1979 and was diligent up to its constructive reduction to practice on August 4, 1980 (A17-20). These holdings, on which the Federal Circuit granted Hybritech an early priority date, were critical as they eliminated major prior art relied on by the trial court in holding the patent invalid.[2]

Hybritech, realizing the Federal Circuit made a *de novo* finding supporting diligence, asserts an alternative ground existed on which the Federal Circuit could base its holding that Hybritech's date of invention (priority) preceded the work of LJCRF and Oi/Herzenberg. In effect, Hybritech is arguing that even if the Federal Circuit violated Rule 52(a), the outcome on the merits would not be affected.

Specifically, Hybritech argues that even if it were not diligent, the LJCRF and Oi/Herzenberg work which the Federal Circuit found to be prior art, was preceded by reductions to practice of the claimed invention at Hybritech in August, September and October, 1979. Contrary to Hybritech's assertions, the Federal

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[2] The trial court held the claimed invention was not conceived or reduced to practice before May, 1980 (A40-41, 46, 48) and concluded the patent was invalid because it had already been invented by LJCRF in November, 1979 and would have been obvious in light of other prior art (A45, 55).

Circuit *did not* hold the claimed invention was reduced to practice in August, September or October, 1979. Rather, it summarized the trial testimony regarding these dates, with respect to diligence (A17-19), concluding, Hybritech was diligent up to its constructive reduction to practice by filing of the patent application (A19-20).

In any event, the August, September and October, 1979 experiments cannot establish reductions to practice, as a matter of law, since they do not possess every element and limitation of the claims. *Correge v. Murphy*, 705 F.2d 1326, 1329 (Fed. Cir. 1983). Specifically, the laboratory notebook entries for August, September and October, 1979, do not disclose the 10^8 1/m monoclonal antibody affinity limitation of the patent claims, alleged by Hybritech to be critical. In addition, the August and September entries do not measure antigen as the claims require.[3] None of the entries depict assays for more than one antigen, hepatitis, and therefore none are generic to all antigens, as required by the claims (B1-B2).

The October 1979 entry neither describes a sandwich assay nor mentions monoclonals. As the Federal Circuit noted, Hybritech *alleged* this to be "a reduction to practice of the claimed invention, but fail[ed] to cite any related testimony or other evidence in support thereof." (A18)

The Federal Circuit did not, and could not "alternatively hold" Hybritech reduced the invention to practice in August, September or October, 1979. Accordingly, the Federal Circuit's finding on diligence and its reversal of the trial court's evaluation of the

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[3] Hybritech's statement, at p.19, that MAB's patent law expert, Ciotti, "admit[ted] Respondent's prior invention through an August 1979 reduction to practice using monoclonal antibodies . . . having the claimed affinity," is false. Rather, Mr. Ciotti testified that the August, 1979 experiment showed a reduction to practice of *one assay*—a hepatitis assay—and that it was not "the making of the invention in terms of, for instance, in Claim 19," since there was no appreciation that the assay could be applied to other antigens, as required by the claims. (See Ciotti testimony at A18, B1-2) Ciotti never testified as to antibody affinity in the August experiment.

evidence on Hybritech's date of invention in violation of Rule 52(a), are critical to evaluating whether the Hybritech patent is valid (A15-21).

III

THE FEDERAL CIRCUIT, IN VIOLATION OF RULE 52(a), OVERTURNED THE TRIAL COURT'S FINDINGS ON LJCRF'S PRIOR INVENTION BASED LARGELY ON AN INDEPENDENT CREDIBILITY DETERMINATION OF DR. RUOSLAHTI

Hybritech asserts the Federal Circuit did not reevaluate the trial court's credibility determination of Ruoslahti. Inconsistently, it sets forth the evidence relied on by the Federal Circuit, at A20-21, to discredit the trial court's credibility determination of Ruoslahti which related to whether LJCRF reduced the claimed invention to practice in November, 1979. Moreover, Hybritech admits the Federal Circuit reevaluated the trial court's credibility finding, by conceding the Federal Circuit "tested Ruoslahti's conclusory statement [that the LJCRF work was reduced to practice in November 1979] with inconsistencies in his own testimony, with the testimony of his co-workers, and with the documentary evidence." (Opp. at p.15) Further evidence of the Federal Circuit's independent credibility finding is its statement that an attempt to provoke an interference proceeding in the PTO by LJCRF was "evidence which bore upon the credibility of Ruoslahti's testimony."[4] (A20)

The Federal Circuit concluded there was "inadequate factual basis for the district court's holding that LJCRF reduced the claimed invention to practice as early as November 1979 . . . ." (A20) The primary evidence on which the trial court relied was Ruoslahti's testimony, which the Federal Circuit implicitly found not credible, and Uotila's notebooks (A20).

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[4] Additional examples of the Federal Circuit's reinterpretation of the LJCRF evidence, contrary to the trial court, are set forth at pp. 15-17 of MAB's Petition.

Summarizing, the trial court considered the record in its entirety and, based on strong documentary and testimonial supporting evidence, held LJCRF had a November, 1979 reduction to practice date. The Federal Circuit reinterpreted the evidence and reevaluated witness credibility *de novo,* in violation of Rule 52(a), reversing the trial court's holding of LJCRF's reduction to practice. In doing so, the Federal Circuit improperly usurped the trial court's important fact-finding role.

Such conduct by an appellate court was condemned in *Inwood Laboratories, Inc. v. Ives Laboratories,* 456 U.S. 844, 856-857 (1982), as a violation of Rule 52(a). In *Inwood,* this Court reversed and remanded the appellate court's decision based on a *de novo* review of the evidence, which disregarded the trial court's findings or implicitly rejected them. *Id.*, 456 U.S. at 857, quoting in part, *United States v. Real Estate Boards,* 339 U.S. 485, 495 (1950).

IV

THE TRIAL COURT ACTED PROPERLY IN PREPARING ITS FINDINGS AND CONCLUSIONS OF LAW

As noted in our Petition, the trial court did not, as Hybritech asserts, merely adopt verbatim MAB's pretrial brief and proposed findings and conclusions. This is graphically illustrated in MAB's Appendix H, (A82-104), which shows the extensive, independently prepared portions of the trial court opinion. The parties submitted post-trial summaries of the evidence, with specific citations to the record, to safeguard against issuing findings and conclusions unsupported by the record. Moreover, the trial judge set forth detailed findings and conclusions, with citations to trial exhibits.[5] Hybritech never objected to MAB's pretrial proposed findings.

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[5] Hybritech criticizes the trial court for insufficient citations to the record. However, as this Court is aware, it is common practice for trial court opinions not to include extensive cites to the record, as long as the findings and conclusions therein are reasoned and supported by the record, as they were here.

Contrary to Hybritech's assertion, this Court has not "condemned" the practice of a trial court's adoption of proposed findings and conclusions of law.

As this Court held in *Anderson*,

> [e]ven when the trial judge adopts proposed findings verbatim, the findings are those of the court and may be reversed only if clearly erroneous.

Anderson v. Bessemer City, N.C., 470 U.S. 564, 572 (1985); *United States v. Marine Bancorporation*, 418 U.S. 602, 615, n. 13 (1974); *United States v. El Paso Natural Gas Co.*, 376 U.S. 651, 656-657 (1964).

It is unreasonable for a trial court, with its busy schedule, to "reinvent the wheel" and therefore entirely appropriate for it to adopt portions of proposed findings and conclusions of law, with which it agrees. Accordingly, this Court has consistently acknowledged the propriety of adopting submitted findings and has mandated that appellate courts apply the standards of Rule 52(a) in review.

V

HYBRITECH DELIBERATELY MISCHARACTERIZES MAB'S PETITION AS AN ATTACK ON JUDGE RICH

Hybritech's accusations that MAB attacked the credibility of Judge Rich, author of the appellate decision, is an obvious ploy intended to direct this Court's attention away from the merits. In emphasizing the importance of this Court's review of the newly created Federal Circuit's application of Rule 52(a), MAB pointed to the unique difficulties that exist for judges on the Federal Circuit who made the transition in 1982 from the predecessor Court of Customs and Patent Appeals (CCPA), which had applied a *de novo* standard of review. In support, MAB cited a speech by Judge Rich, a judge on the CCPA for over 25 years, where he also acknowledged the different standards of review and the difficulty he personally realized in applying the deference mandated by Rule 52(a). Hybritech's false sensationalism is truly unfortunate.

MAB realizes and appreciates the tremendous contribution Judge Rich has made to patent law. But, the intent of the Federal Circuit judges, which obviously is to follow Rule 52(a) as is clearly stated in the Federal Circuit's opinion, is not the issue. Rather, the issue is whether the standards of Rule 52(a) are in fact being followed.

VI

HYBRITECH HAS ARGUED EVIDENCE, OUT OF LEGAL CONTEXT, IN AN ATTEMPT TO SUPPORT THE FEDERAL CIRCUIT'S HOLDING OF PATENT VALIDITY

A. That Monoclonal Sandwich Assays Are an Improvement Over the Then Commercially Available Polyclonal Tests Is Not Dispositive of Patentability

Hybritech refers to MAB's statements that the monoclonal sandwich assay has advantages over previously commercially available tests as evidence of patentability. (Opp. at 23) But, the proper inquiry regarding patentability is: *what causes* a monoclonal sandwich assay to be better than prior commercial products.

Evaluating improvements as evidencing patentability was explained by this Court in *Hotchkiss v. Greenwood*, 52 U.S. 248 (1851), wherein an improved doorknob was deemed better because of the inherent superiority of a newly substituted material. This Court concluded "this, of itself, can never be the subject of a patent." *Hotchkiss*, 52 U.S. at 266. (Petition, p.23, n.19)

The antithesis situation is shown in *United States v. Adams*, 383 U.S. 39 (1966), cited by Hybritech, wherein Adams invented the first practical water-activated battery. This Court, in affirming the validity of Adams' patent, considered the following factors. First, the prior art suggested that Adams' battery would not work. Second, Adams' battery had "wholly unexpectedly" operating advantages. 383 U.S. at 51.

Factually, *Adams* is far removed from the present case wherein, once Drs. Kohler and Milstein developed a method for mass producing monoclonal antibodies, it was suggested by the industry

that substituting monoclonals for polyclonals in existing assays would have significant advantages. Moreover, once monoclonals were substituted for polyclonals by Hybritech, MAB, and others in the field, the expected benefits were in fact realized. While admittedly an improvement over the polyclonal sandwich assay, no "wholly unexpectedly" results, as in *Adams*, were realized.

The trial court realized Hybritech's invention was based on a substitution of reagents, monoclonals for polyclonals (A38, 45). It then evaluated the assay's superiorities in light of the inherent properties of the substituted reagent (monoclonals) (A43, 45). The Federal Circuit's statement that, as a matter of law, such an inquiry is inappropriate (A28), is directly contrary to this Court's precedents, which were codified in § 103 of the present Patent Statute, and requires correction. (Petition, pp. 22-24)

B. The Trial Court Never Relied Upon an "Obvious to Try" Analysis as the Section 103 Standard of Patentability

Hybritech's repeated allegation that MAB is arguing "obvious to try" as the appropriate standard or test of patentability is false. Rather, MAB acknowledged the propriety of the trial court's inquiry into whether the claimed invention, a monoclonal sandwich assay, was suggested by the prior art.

The consideration for this Court is the appropriateness of the Federal Circuit's practice of ignoring this evidence and the evaluation thereof by the trial court by labelling it as "obvious to try" evidence. Yet, whether the prior art suggested the claimed invention, an analysis *approved and recommended* by the Federal Circuit, is substantively identical to the inquiry of whether, in light of the prior art, it would be obvious to try the claimed invention. Accordingly, evaluating whether prior art suggesting the claimed invention, and relied on by the trial court, should be given no weight on appeal simply by being termed "obvious to try" evidence, is an important reason why this Court should grant Certiorari in this case.

VII

THE FEDERAL CIRCUIT SHOULD HAVE REMANDED THE DILIGENCE ISSUE SINCE THE EVIDENCE DID NOT LEAD TO ONLY ONE CONCLUSION

Since diligence is based heavily on credibility evaluations requiring corroboration, and in light of the fact that the parties vigorously contested that evidence, the Federal Circuit should have remanded the issue of diligence. Hybritech incorrectly argues it was appropriate for the Federal Circuit to make a *de novo* finding on diligence (A19), because the record will permit only one conclusion.

In order to establish diligence, an inventor must account for the entire critical period (starting any time after conception of the claimed invention but before the effective date of the prior art and ending in reduction to practice) by showing either activity aimed at reduction to practice or legally adequate excuses for inactivity. At trial, Hybritech entered into evidence numerous experiments, primarily in the form of notebooks, carried out between January, 1979, and May, 1980 as evidence of conception or reduction to practice. MAB disputed Hybritech's allegations, even of conception, since Hybritech did not establish possession of each and every element of the claimed invention prior to May, 1980. By strenuously arguing there was no conception prior to May 1980, long after the effective date of the most pertinent prior art, MAB also implicitly argued there was *no diligence* prior to May, 1980. The trial court agreed. Thus, Hybritech's assertion that MAB did not dispute diligence during the critical period is incorrect.[6]

Hybritech admits that inventor David testified for approximately a day and a half explaining and describing the documents it submitted to establish conception, diligence and reduction to

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[6] Hybritech's criticism of MAB for not asking for a remand before the Federal Circuit completely ignores the fact that Hybritech appealed and MAB only requested, as was entirely appropriate, that the court affirm its victory below. To suggest MAB had a duty to request a remand on appeal, in light of the fact it was the prevailing party before the trial court, is absurd.

practice. The documentary evidence introduced was necessary to support David's testimony of priority which is inherently "highly suspect". *Bell Tel. Laboratories, Inc. v. Hughes Aircraft, Co.*, 564 F. 2d 654, 657 (3rd Cir. 1977), *cert. den.* 435 U.S. 924 (1978). In other words, "the function of the corroborating evidence is to assist the fact finder in deciding whether the inventor's testimony is *credible*." Id. (Emphasis added).

The Federal Circuit's finding of diligence, spanning a 19-month period (from Janurary, 1979 to filing in August, 1980), is especially surprising in light of its own case law precedents where much shorter periods of time were deemed too long. *In re Mulder*, 716 F.2d 1542, 1545 (Fed. Cir. 1983) (the court held that diligence needed to be established for even a two-day period); *Gould v. Schawlow*, 363 F.2d 908, 920-921 (CCPA 1966) (failed to prove diligence over an 8 month period); *Brown v. Barton*, 102 F.2d 193, 198 (CCPA 1939) (failed to prove diligence over a 5 week period); *Ireland v. Smith* 97 F.2d 95, 97 (CCPA 1938) (failed to prove diligence over a 25 day period).

CONCLUSION

For the reasons set forth in MAB's Petition and Reply Briefs, this case presents a unique combination of important substantive and procedural issues requiring review by this Court.

Dated: March 20, 1987

Respectfully submitted,

FLEHR, HOHBACH, TEST,
ALBRITTON & HERBERT

By DAVID J. BREZNER
Attorneys for Petitioner
Monoclonal Antibodies, Inc.

There was a monoclonal, namely, identified in here as Number 68, which was substituting all the various combinations with the polyclonal and without it. And it indicates that counts were read.

There is no indication that there was ever any antigen measured. And the part bracketed in orange there requires the measuring either of the amount of labelled antibody bound or the amount of unreacted labelled antibody. So there is no measuring of any amount here.

Also, of course, it is limited to—it is limited to hepatitis antigen.

And without a generic conception, it would just be merely a—if it did work for its intended purpose—which I would assume for the purposes of discussion—it would be a reduction to practice of one embodiment.

And without a corresponding generic conception, I don't think it could be held to be the making of the invention in terms of, for instance, in Claim 19.

Q. What do you mean by generic conception, and why is that required?

A. One must conceive of the invention in terms of which it is claimed. As I illustrated in the typical situation where inventors make inventions, they are encouraged to write down the invention in very generic terms.

If they do not do that—for instance, there is no reason why Hybritech couldn't invent, for instance, a monoclonal antibody assay for hepatitis and limit it to hepatitis, and that would be it.

And that's all this really does is it shows a reduction to practice of a hepatitis assay. If there is no appreciation that it can be applied to other antigens, then it is limited to that.

That's why you need the additional conception of something generic in order to be able to say this is that invention. It is just an embodiment of that invention.

Q. Thank you. Do you have an opinion on the issue of obviousness, 103 obviousness, in this case?

A. Yes, I do.

Q. What is that opinion?

A. I believe that the claimed invention is obvious under 103.

Q. What are the reasons for that opinion, Mr. Ciotti?

A. Well, there are quite a few reasons. There are several pieces of art that were not before the Patent Office.

I also think that—well, one was cited in the patent, but there is no indication the examiner ever looked at it.

Q. You feel there was more relevant art than what was before the examiner that existed?

A. Yes.

Q. Could you please explain that?

A. I think the Oi and Herzenberg article is more relevant.